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LITHIATION REACTIONS OF 3-(4-CHLOROPHENYL) SYDNONE AND 3-(4-METHYLPHENYL) SYDNONE

A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science

By

NIGEL NGONIDZASHE CHITIYO
B.S., University Of Zimbabwe, 2002

2009
Wright State University

WRIGHT STATE UNIVERSITY
SCHOOL OF GRADUATE STUDIES

November 12, 2009

I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY Nigel Chitiyo ENTITLED Lithiation reactions of 3-(4-chlorophenyl) sydnone and 3-(4-methylphenyl) sydnone BE ACCEPTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF Master of Science.

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Abstract

Chitiyo, Nigel M.S., Department of Chemistry, Wright State University, 2009.
Lithiation reactions of 3-(4-chlorophenyl) sydnone and 3-(4-methylphenyl) sydnone.

Ortho-iodophenyl sydnones are key intermediates in Sonogashira coupling reactions and the resulting *ortho* alkynyl sydnones are useful precursors to functionalized sydnonquinolines. In this work, three synthetic routes leading to the synthesis of these versatile intermediates were explored.

Lithiation reactions of 3-(4-chlorophenyl) sydnone and 3-(4-methylphenyl) sydnone followed by trapping with iodine electrophiles yielded the expected disubstituted species 3-(4-chloro-2-iodophenyl)-4-iodosydnone and 3-(4-methyl-2-iodophenyl)-4-iodosydnone in yields ranging from 14% to 75%. Subsequent reduction with sodium sulfite removed the iodine at the C-4 position in both species yielding the *ortho* iodophenyl sydnones in 80% and 85% yield, respectively.

A surprising result was the discovery that careful reduction of 3-(4-chloro-2-iodophenyl)-4-iodosydnone and 3-(4-methyl-2-iodophenyl)-4-iodosydnone using sodium borohydride could generate the corresponding versatile *ortho* iodophenyl sydnones in 70% and 97 % yield, respectively.

Even more surprising, was the realization that careful manipulation of reactant quantities and physical parameters could generate the desired *ortho*-iodophenyl sydnones in yields ranging from 49% to 73% in a one step lithiation reaction. Interestingly, selective and non-selective desilylation of trisilylsydnones as well as disilylsydnones could be achieved using potassium carbonate or tetrabutylammonium fluoride.

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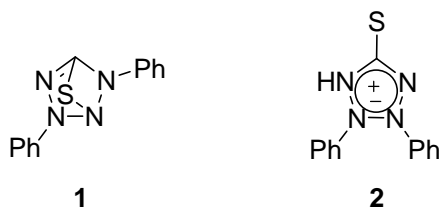
I also want to express my sincere gratitude to my family here and back home in Zimbabwe, especially my parents, Abisha and Violet Chitiyo as well as my brother Dexter Chitiyo for their psychological and financial support throughout my educational career.

Finally, I have appreciated the help of all of the students, Chemistry Department faculty and staff for their help in the classroom, laboratory, and for making me feel at home.

Introduction

Foreword

Towards the end of the nineteenth century Emil Fisher¹ reported the formation of an orange crystalline compound, dehydrodithizone, from the oxidation of dithizone. As more information on the chemical and physical properties became available it was evident that the bicyclic structure **1** he had proposed initially was incompatible. The structure that was deemed acceptable was a resonance stabilized monocyclic, mesomeric, ionic dipolar species **2**. The supporting evidence for the existence of mesomeric ionic (mesoionic) structures was provided by Baker, Ollis and Poole²⁻⁴ in their articles published in the late 1940s and early 1950s.

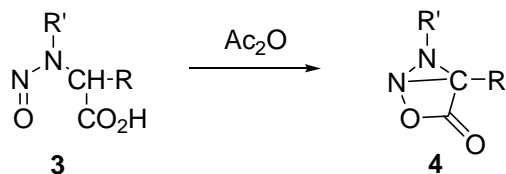


Sydnones are the most studied members of the class of mesoionic compounds. They have interesting physical, chemical and biological properties. Since their discovery, sydnones have fascinated many scientists and have generated considerable research interest. Several reviews have been published relating to these compounds⁵⁻¹², and our lab has seen a number of MS graduate students present their theses on various explorations and manipulations of arylsydnones.¹³⁻²³ The reader is referred to the following review,

which highlights some significant achievements that have been accomplished with regards to sydnone research, as well as important discoveries that have come from our lab over the years.

Historical

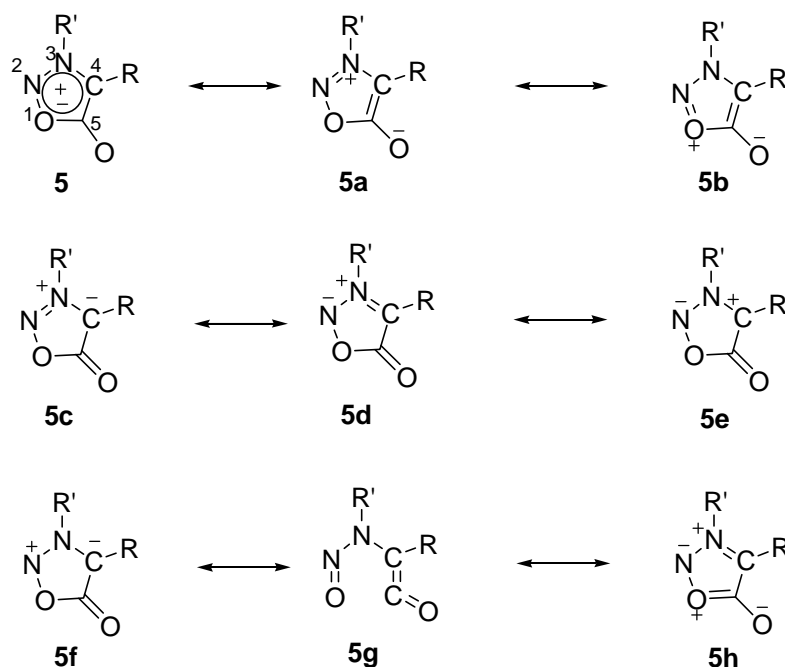
Sydnone were first synthesized in Sydney, Australia in 1935. When Earl and Mackney²⁴ treated N-nitroso-N-phenylglycine with acetic anhydride they obtained a neutral anhydro derivative to which they assigned a bicyclic structure **4** (R'=Ph, R=H). Slightly modified analogues of this proposed structure were later synthesized, resulting in a set of structures popularly termed 'sydnone' by virtue of their discovery in Sydney, Australia.



However the assigned bicyclic structure was met with skepticism and was later disputed following solid arguments put forward by Baker, Ollis and Poole^{2,3}. For instance, the cyclization of the N-nitroso-N-arylglycines **3** (R=H, R'=Ph) with acetic anhydride and the subsequent hydrolysis of the sydnone under basic conditions returned the starting N-nitroso species, a result which could not be attributed to the five-membered proposed bicyclic structure. The strained stereochemistry of the latter was also in sharp contradiction to its formation from acetic anhydride at low temperatures. The structure proposed by the three authors that later became accepted, was a monocyclic, resonance stabilized dipolar oxadiazolone derivative hybrid with many canonical forms (**5a-h**).

Sydnones were thus categorized as unique mesoionic (mesomeric ionic) compounds.

Compounds that fit this classification must possess the following characteristics: 1) should have delocalized positive and negative charges, 2) have a planar five membered heterocyclic ring containing an exocyclic atom or group with considerable charge density and 3) possess considerable resonance energy⁴.



The three characteristics aforementioned can be used to distinguish mesoionic compounds from formally related dipolar species like ylides and zwitterions where a great deal of charge localization is observed. In mesoionic systems charge distribution is delocalized resulting in more than one resonance form.

Sydnones are derivatives of 1, 2, 3-oxadiazoles, however, since 1, 2, 3-oxadiazoles are known to exist as open chain congeners, it appears that sydnones are unique in that they

are the only cyclic derivatives in this class. The term 'sydnone' is therefore specific to cyclic oxadiazole derivatives and is the name used by Chemical Abstracts in classifying these compounds.

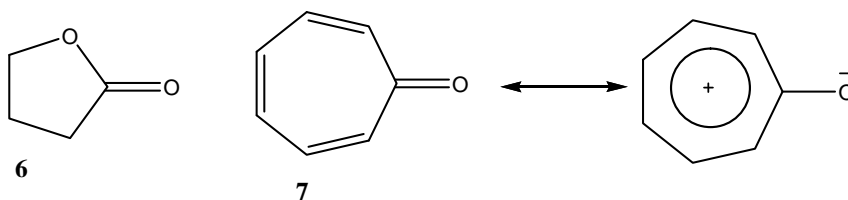
Physiochemical Properties and Electronic Structures.

Sydnones are stable compounds of considerable polarity. Arylsydnones are generally solid crystals whereas alkylsydnones are usually either low melting point solids or liquids and can be distilled *in vacuo* without appreciable decomposition. They readily dissolve in polar organic solvents but are insoluble in nonpolar solvents like hexane and ether. In water they are generally insoluble but their solubility is enhanced when a polar functional group is present within the molecule.

The distinguishing features of sydnones can be demonstrated through their characterization using spectroscopy, particularly, Infrared and NMR spectroscopies. Sydnones show a strong carbonyl stretch at $\sim 1730\text{-}1760\text{cm}^{-1}$ and a medium intensity C-H stretch absorption at $\sim 3150\text{cm}^{-1}$ corresponding to the C-4 ring position (when present)²⁵⁻²⁸. This C-H absorption associated with the C-4 position (when present) distinguishes sydnones from alkyls, aryls and epoxides with a similar ring strain, which show a different absorption at around $2900\text{-}3050\text{cm}^{-1}$. In an unresolved structure, this absorption is very useful in determining whether or not the C-4 position is substituted. The sydnone carbonyl stretch usually shows up as a single strong band. However, due to Fermi resonance splitting in some cases multiple bands have been observed^{29, 30}. In addition, as already stated, the sydnone carbonyl typically appears at $\sim 1730\text{-}1760\text{cm}^{-1}$ but, in

comparison with congeneric carbonyl containing species such as γ -lactone **6** [which absorbs at 1770cm^{-1}] and tropone **7** [which absorbs at 1638cm^{-1}], one might conclude that the exocyclic C=O bond at the sydnone C-5 position is closer in length to that of a double bond than a single bond^{29, 30}.

NMR spectra show that the proton at the C-4 position of the sydnone ring (when present) is greatly shielded and usually appears between 6.5-7.5ppm depending on the solvent used.

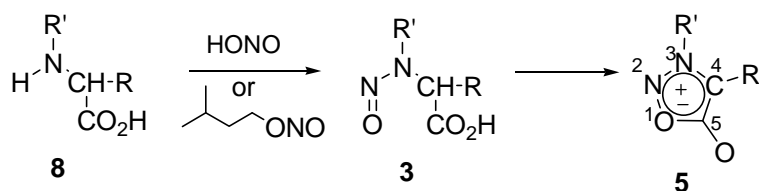


The carbonyl nature of the C-O exocyclic bond is further supported by X-ray crystallographic analysis of various 3-substituted and 3,4-disubstituted sydnones which shows that this C=O bond is closer in length to that of a double bond. However, integrated absorption measurements suggest that a high degree of carbonyl bond polarization, rather than bond strength, is responsible for the relatively high energy of absorption. Additionally molecular orbital calculations and vibrational force constants obtained from vibrational spectra indicate a π -bond order of the sydnone carbonyl lower than those for alicyclic esters³¹ thus supporting the argument that contributions from other vibrational modes cause the sydnone carbonyl group to absorb at a higher frequency than anticipated. In addition, there is evidence from spectroscopic and theoretical studies that the protonation of the sydnone moiety occurs at the exocyclic

oxygen.³²⁻³⁶ This reinforces earlier observations in which bond orders and charge densities were correlated to the calculated observed dipole moments and the observed UV maxima.^{37, 38} These studies support the earlier contention that substantial charge density resides on the exocyclic oxygen.

Synthesis

The synthesis of sydnones is achieved through the traditional route; *via* the cyclodehydration of N-substituted N-nitroso- α -amino acids (*cf.* **3**). The R substituent can be an alkyl, aryl or hydrogen, but the R' substituent has to be alkyl or aryl since if R' is a hydrogen, prototropy occurs leading to a neutral species. The N-nitrosoaminoacid **3** is, however, prepared generally *via* nitrosation of an N-substituted glycine **8** with nitrous acid. However, for some sydnones with acid sensitive groups the method has to be modified slightly. The use of isoamyl nitrite and dimethoxymethane ensures the desired neutral reaction conditions, thus making it possible to obtain some otherwise unattainable sydnones.³⁹



The original cyclodehydration used by Earl and Mackney made use of acetic anhydride at room temperature for six days. Variations to this method have been found however and these include: heating in acetic anhydride or thionyl chloride; treatment with phosphorus pentoxide or the use of trifluoroacetic anhydride (TFAA).

The most widely used method is the cyclization with TFAA. It is rapid (<15minutes), is achievable at low temperatures (-5°C to 0°C) and affords high yields (>90% for N-phenylsydnone). The only setback is the high cost of TFAA in comparison to other reagents.

Other synthetic strategies for the cyclization include using: (1) acetic anhydride at room temperature facilitated by ultrasonification⁴⁰ (2) haloiminium salts⁴¹ (3) N, N-dimethylchlorosulfitemethanium chloride⁴² and (4) 2chloro-1, 3-dimethylimidazolinium chloride⁴³. However, the use of TFAA has continued to be the preferred method since it achieves fast, efficient and reliable cyclization.

Chemical and Biological behavior

Studies have shown that the sydnone ring possesses a distinct aromatic nature and a dichotomy in electronic effects. These characteristics are reflected in the chemical behavior of sydnones as has been illustrated in previous work. For instance a great deal of work has been done to show that sydnones undergo electrophilic aromatic substitution at the C-4 position of the ring (cf. **5**, R=H).⁴⁴ These electrophilic substitution reactions display the aromaticity of the sydnone ring since an intrinsic property of any aromatic system is to undergo electrophilic substitution with retention of aromaticity. Electrophilic aromatic substitution reactions of sydnones typically include halogenation, nitration, acylation and sulfonation. The high regioselectivity of these reactions (even when an aryl group is attached to the N-3 position) has been attributed to two factors: (1) the considerable partial negative charge that resides at the C-4 position appears to activate

this position; and (2) the considerable partial positive charge that resides at the N-3 position seems to deactivate the juxtaposed aryl ring.

In the case when activating groups are attached to the aryl ring at the N-3 position, these may allow the aryl moiety to compete successfully for the electrophile, thus opening avenues to a variety of sydnone derivatives. This premise has been used in both bromination and nitration.^{45,46}

Sydnes are also useful precursors to hydrazines²⁴, and can be utilized as 1,3-dipoles in cycloaddition reactions^{47, 48}. They can be used as electrolytic solvents for non-aqueous batteries⁴⁹ and facilitate micelle production in molecular aggregation⁵⁰. However, even though sydnones have many potential applications, most researchers have been motivated by their potential biological applications. These include their potential use as antifungal, anti-inflammatory⁵¹, analgesic, antibacterial and anti tumor prodrugs.⁵² In addition; sydnones have liquid crystal properties⁵³, have been incorporated into azodyestuffs⁵⁴⁻⁵⁷ and have been experimentally tested for use as lithium battery electrolytes.

Reactions of Sydnones

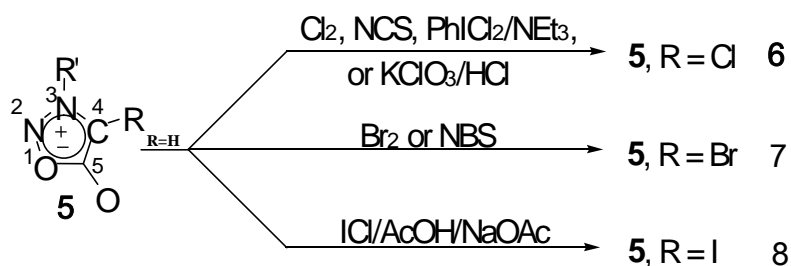
1. Aromatic Substitution Reactions of Sydnones.

Sydnones with a proton attached at the C-4 position (cf. **5**, R=H) can undergo electrophilic aromatic substitution reactions at this position. The same electrophiles typically employed in substitution reactions of benzene and other related arenes can be used to substitute the proton at the 4-position of sydnones owing to the high negative

charge density at this C-4 position. Sydnonees thus undergo sulfonation, nitration, acylation, halogenation and metallation. These substitution reactions are discussed below.

A. Halogenation of Sydnonees.

The halogenation of sydnones (cf. **5**) can be attained through several pathways. When sydnones such as **5** (R=H) ⁵⁸⁻⁶⁰ are treated with chlorine, potassium chlorate in moderately concentrated HCl ⁶¹, dichloriodobenzene with triethylamine ⁶² or N-chlorosuccinimide (NCS) ⁶³, the corresponding chlorinated sydnones (cf. **5**, R=Cl) are obtained. Sydnones brominated at the C-4 position, (cf. **5**, R=Br) can be attained by reacting the sydnone, **5** (R=H) with bromine ⁵⁸⁻⁶⁰, or N-bromosuccinimide (NBS) ⁶³. 4-Iodosydnones (cf. **5**, R=I) can be obtained through the use of iodine monochloride in acetic acid at room temperature ⁶⁴. However, their synthesis is more difficult in comparison to bromination and chlorination.



Since sydnones appeared to be brominated easily at the C-4 position, researchers postulated that the 4-bromo moiety (cf. **5**, R=Br) could be used as a protecting group for the sydnone ring. ⁶⁵The removal of this bromine can be accomplished by treating the brominated sydnone with sodium borohydride or sodium dithionite in methanol. ⁶⁶ These

two complementary methods effectively debrominate the bromosydnone in a very regiospecific way and require less stringent conditions compared to previous methods. However, the two methods also have their limitations and deficiencies, which include the tendency for sodium borohydride to react with pendant functional groups like aldehydes, ketones, esters or carboxylic acids and the susceptibility of sodium dithionite to steric factors. The use of activated zinc under ultrasonification⁶⁷ to attain debromination, as reported by Tien and coworkers, is not successful when strong electron withdrawing groups are present, thus the approach of choice is the use of sodium sulfite⁶⁸ which is not prone to any of the disadvantages mentioned above.

B. Nitration.

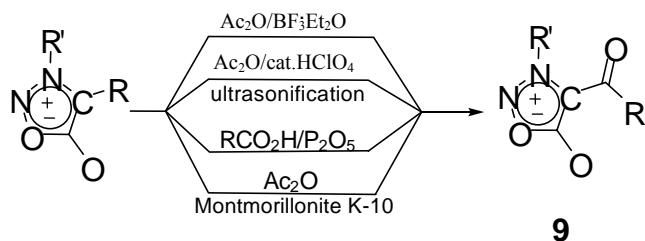
Very little research has been done on the nitration of sydnones owing to the strongly acidic conditions required for this reaction. However, 3-phenylsydnone (**5**, R=H, R'=Ph) reacts with potassium nitrate in the presence of sulfuric acid at -5 °C to yield a relatively unstable 4-nitroderivative **5** (R = NO₂, R' = Ph) in modest yield.⁶⁹

C. Acylation and Carboxamidation.

A previous report⁷⁰ had suggested that it was not possible to acylate 3-phenylsydnone **5** (R = H, R' = Ph) with either acetic anhydride or benzoyl chloride in the presence of a Lewis acid catalyst. Yashunskii and co-workers however showed that this transformation is possible and obtained the 4-acetyl derivative **9** (R = Me, R' = Ph) using acetic anhydride and boron trifluoride etherate.⁷¹ In addition, Tien and coworkers have acylated various substituted sydnones using acetic anhydride and HClO₄ or H₃PO₄.⁷² Greco and

coworkers⁷³ have reported that a similar transformation can be attained through heating various 3-substituted sydnones in the presence of a carboxylic acid and P₂O₅.

Nevertheless, it was noted that neither aryl nor aralkyl acids reacted; hence the scope of the reaction is limited,

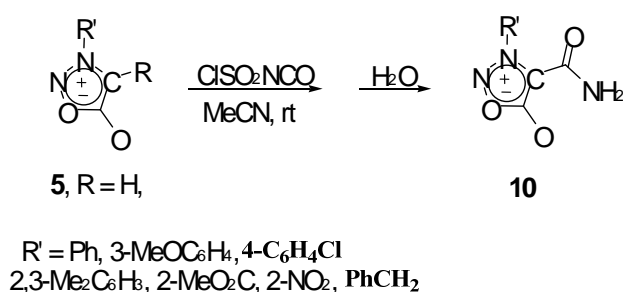


More recent research has shown that 4-acylsydnones can be prepared in a two step process from a cuprosydnone (see Metallation of sydnones section). Tien and coworkers⁷⁴ have demonstrated that ultrasonification of 3-substituted sydnones in the presence of acetic anhydride and a catalytic amount of perchloric acid will afford the 4-acylated derivative quickly in moderate yield. 4-Acetyl derivatives of 3-substituted sydnones also have been obtained *via* the use of acetic anhydride and a catalytic amount of Montmorillonite K-10 at elevated temperatures.⁷⁵ This method is useful in that the catalyst used can be easily removed and disposed of. However, one disadvantage is that the method is slow or unsuccessful with compounds containing electron-withdrawing groups *ortho* to the sydnone ring.

All of these acylations suffer from the limitation that acetic anhydride is used as a solvent as well as reagent. Accordingly, Turnbull and Fisher examined acylation with catalytic amounts of reagent and lower quantities of the acylating agent.²³ With various 3-

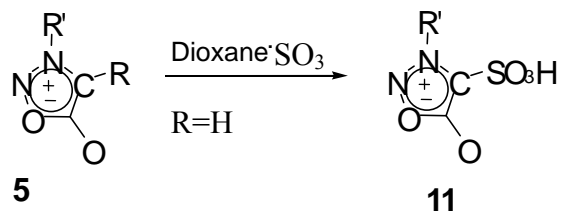
arylsydnone (**5** R=H, R'=Ar) it was shown that good yields of 4-acylsydnone could be obtained with 40 mol% LiClO₄/Bi(OTf)₃ and 4 equivalents of Ac₂O.

In the past, 4-carboxamido sydnone species **10** have been made by a multistep process involving abstracting the sydnone ring proton with butyllithium, treatment with carbon dioxide and subsequent conversion to the acid chloride followed by reaction with ammonia. In recent years, a new method of carboxamidation at the sydnone 4-position has been developed.⁷⁶ By use of chlorosulfonyl isocyanate in acetonitrile at room temperature, Turnbull, Gross and Hall prepared 4-carboxamido sydnone in good yields, directly from a variety of 3-substituted sydnone.



D. Sulfonation.

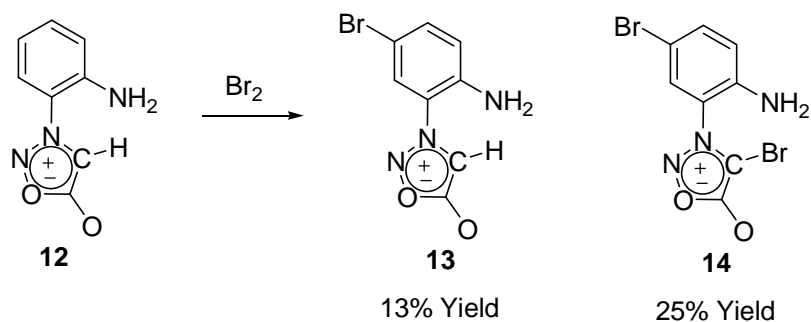
Yashunskii and co-workers have reported the direct sulfonation of a variety of 3-substituted sydnone.⁷⁷ Therein, it was shown that the treatment of sydnone **5** (R=H) with dioxane-sulfur trioxide complex (SO₃) in CH₂Cl₂ at 20°C to 40°C generated the sulfonated derivatives **11**, (R' = 4-MeO- or 4-EtOC₆H₄), which were characterized as either the barium or S-benzylthiuronium salts. However, all attempts to isolate these compounds as the free acid via neutralization were unsuccessful and resulted in the isolation of the non-sulfonated sydnone **5** (R=H).



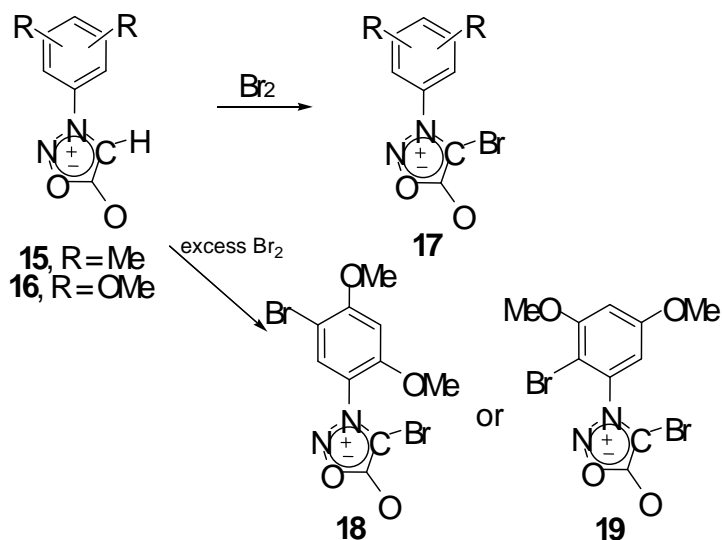
E. Electrophilic Substitution at the Aromatic ring of 3-Arylsydnone.

3-Arylsydnone generally react with electrophiles at the sydnone C-4 position. This is so since a considerable partial negative charge resides at this position. The partial positive charge at the N-3 position apparently deactivates the juxtaposed aryl moiety.

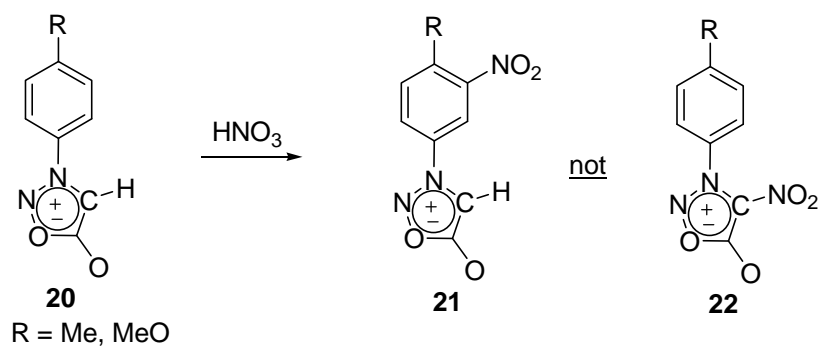
Numerous attempts at bromination of 3-aryl sydnones previously yielded only 4-bromo analogs. However, recent investigations focused on the idea of using an activated 3-aryl sydnone, *e.g.* 3-(2-aminophenyl)sydnone (**12**) to generate a competitive situation for reaction with electrophiles. The preferential substitution sought was for aryl rather than sydnone C-4 substitution. The results as reported showed that the major products were derived from aryl ring substitution and are 3-(2-amino-5-bromophenyl) sydnone (**13**) and 3-(2-amino-5-bromophenyl)-4-bromosydnone (**14**). Hence, for the first time it was demonstrated that the aryl moiety could compete with the sydnone ring for electrophilic substitution. Interestingly when NBS was added slowly to **12**, only **13** was formed in 70% yield.⁴⁵



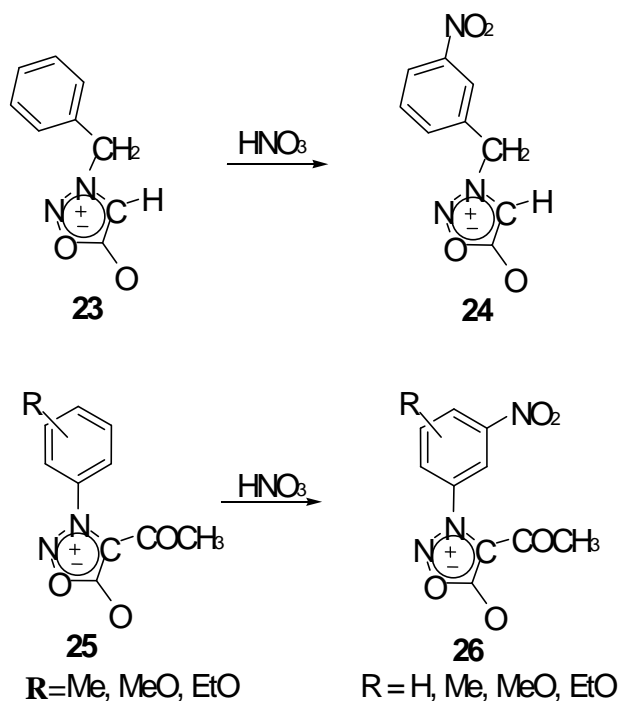
Further examination of this methodology via the bromination of a series of dimethylaryl or dimethoxyarylsydnone (**15** and **16** respectively) with 1 equivalent of bromine occurred only at C-4 position of the sydnone ring (leading to **17**).⁷⁸ In fact even when treated with excess bromine, only the most activated sydnone, the 3-(2, 4- and 3, 5- dimethoxyphenyl) derivatives **16** were brominated on the aryl ring, and only *after* bromination had occurred at the C-4 position. This latter situation is illustrated by the conversion of **16** (R=2,4 diMeO and 3,5 diMeO) to the bromo congeners , **18** and **19** respectively.



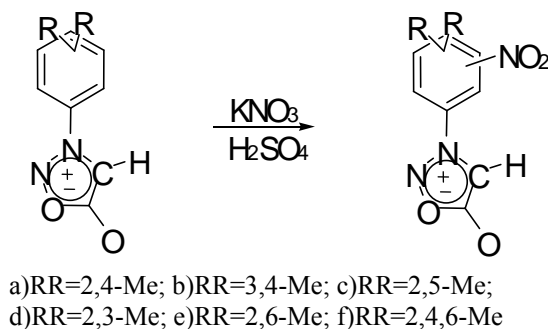
In contrast to the situation with bromination, the nitration of activated 3-arylsydnonees preferentially occurs at the aryl moiety and not at the sydnone C-4 position. Thus, it has been shown that when exposed to nitrating conditions activated aryl sydnones (cf. **20**) afford the product of nitration **21** and not the anticipated 4-nitro derivatives **22**.⁴⁶



More recent research done by Tien and coworkers^{40, 79} showed that the meta nitroaryl products **24** and **26** were obtained when either 3-benzyl **23** or various activated 3-substituted-aryl-4-acetyl sydnones **25** were treated under nitrating conditions. In the latter case, the acetyl group could be removed subsequently with barium hydroxide.



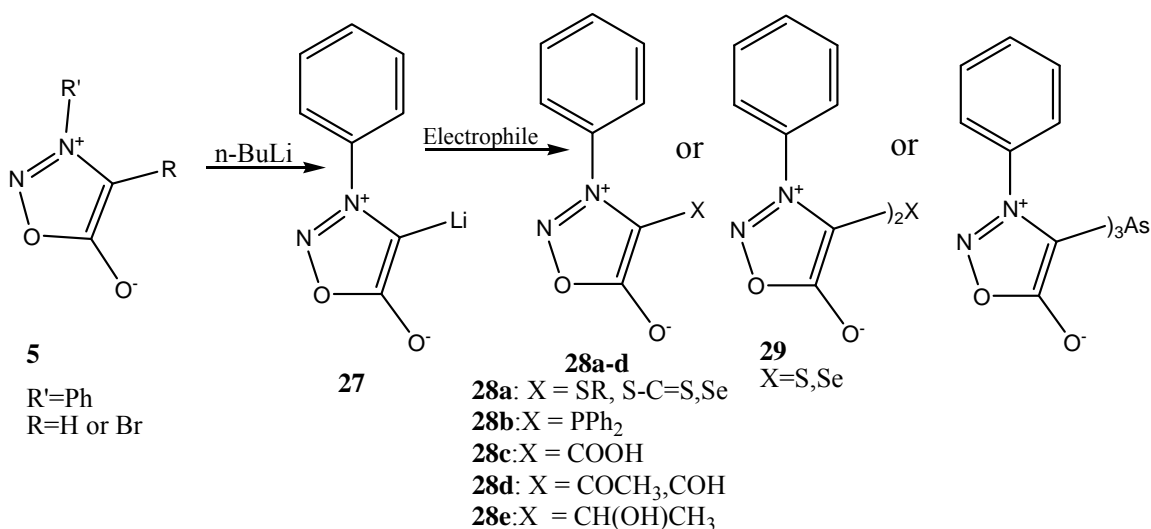
Most recently, Turnbull, Blackburn and Miller⁸⁰ have examined nitration of 3-arylsydnone with multiple electron donating methyl groups on the aryl ring. Once again exclusive aryl ring nitration was observed with a strong tendency for nitration *meta* to the sydnone ring. If the nitration was forced to occur between two substituents on the aryl ring, the favored position was between the sydnone ring and a methyl group, not between two methyl groups.



1. Metallation of Sydnones

The metallation of sydnones has been the most investigated route for substitution at the sydnone C-4 position. Metal complexes which have been prepared and investigated include 4-lithio, 4-cupro, 4-chloromercurio and the 4-palladium(0)⁸¹ or nickel (II) species.⁸²

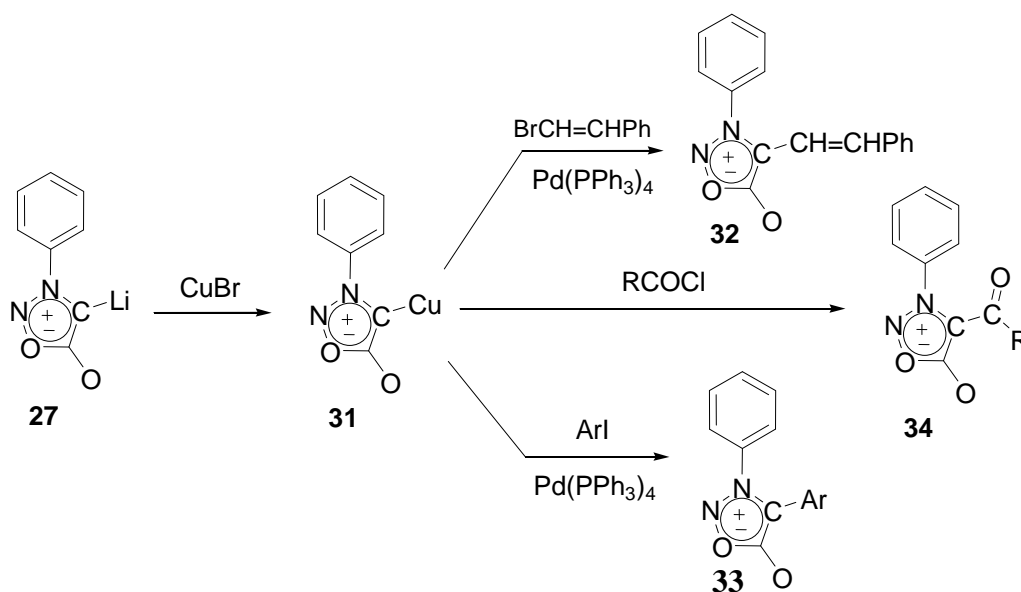
The 4-lithio species (cf. **27**) can be prepared either directly from 3-phenylsydnone **5** (R=H, R'=Ph) or indirectly from metal-halogen exchange of 4-bromo-3-phenylsydnone **5** (R=Br, R'=Ph). This species appears to be the most versatile of all 4-metallo substituted sydnones in terms of its applications.



It is now known that **27** reacts with alkyl or aryl disulfides or diselenides to afford the 4-sydnosulfides or 4-sydnoselenides and derivatives **28a**.⁸³ Additionally, the bis-sydnonyl sulfide and selenide **29** can be prepared in an analogous manner by treating **27** with the appropriate dicyano disulfide or diselenide.⁸³ Extension of this methodology to arsenic trichloride or diphenylchlorophosphorane⁸³ resulted in the preparation of the

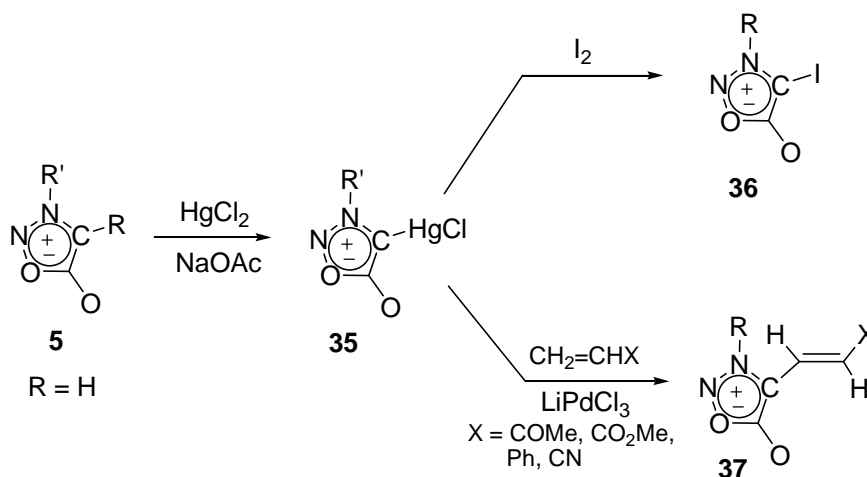
corresponding sydnonylarsine **30** or phosphine **28b derivatives**, respectively. More recently, different types of 4-carboxysydnone **28c** have been prepared by carboxylation of **27** with carbon dioxide.⁸⁴ Additionally, Tien and coworkers⁷⁴ have shown that various 3-substituted sydnones can be lithiated and exposed *in situ* to either N,N-dimethylformamide or acetaldehyde to yield the corresponding acylated **28d** or hydroxylated **28e** derivatives respectively.

The reactivity of the sydnone metal species can be modulated by changing the metal present at the 4-position. A relatively stable sydnonyl cuprate **31** can be obtained by reacting 3-phenylsydnone **5** (R=H, R'=Ph) with butyl lithium and subsequent exposure of intermediate **27** to cupric bromide. This species can be coupled to vinyl or aryl halides over a Pd (0) catalyst to yield the 4-alkenyl **32** or 4-arylsydnone **33**⁸⁵, respectively.



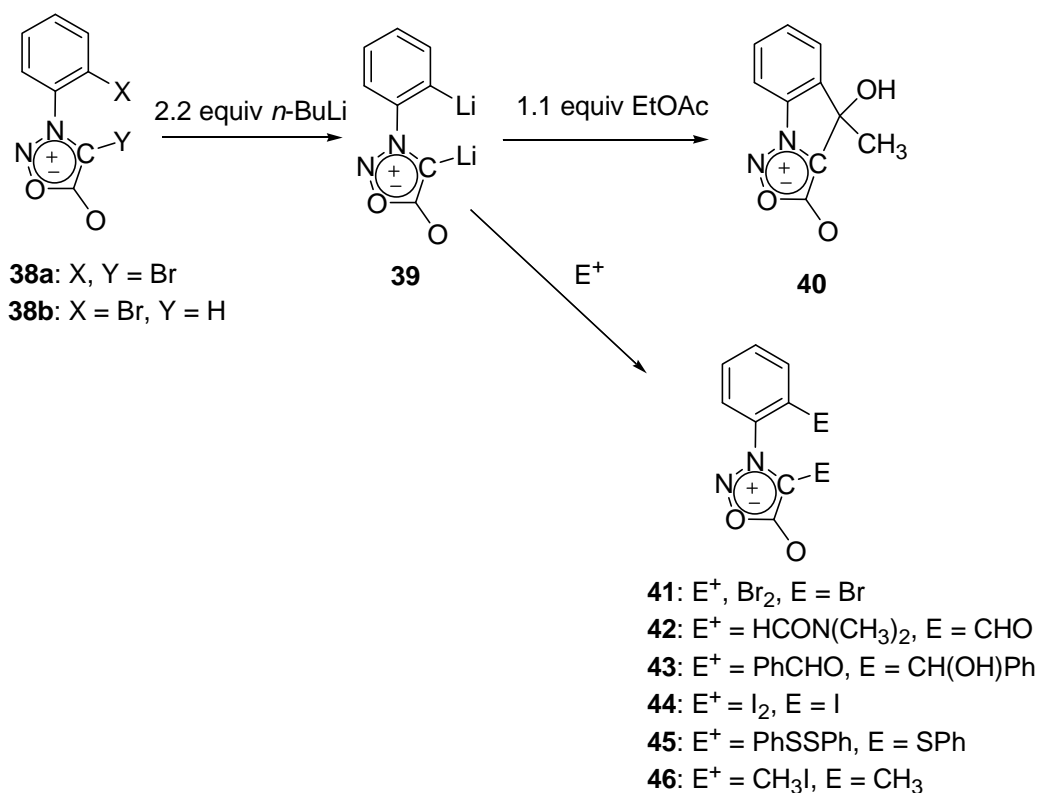
When the sydnonyl cuprate **31** is reacted with more reactive alkyl or aryl acid chlorides the corresponding 4-substituted derivatives **34**⁸⁶ are obtained without the use of the palladium catalyst. More recently, Kalinin and coworkers⁸⁷ have shown that sydnonyl cuprates **31** can undergo palladium catalyzed cross coupling reactions with either heteroaryl iodides or alkynyl bromides to afford the corresponding 4-substituted sydnones in good to excellent yields.

One pathway to effect the substitution of iodine or electron deficient olefins to the C-4 position of the sydnone ring involves the intermediate 4-chloromercurio species **35**. This species is obtained when 3-arylsydnone **5** ($R=H$, $R'=Ar$) are treated with mercuric chloride and sodium acetate in aqueous methanol at ambient temperature.⁸⁸ The intermediate can then be treated with iodine to afford the 4-iodo derivatives **36**. More recently Kalinin reported that reaction of the 4-chloromercurio intermediate with electron deficient olefins produced high yields of only the *trans* isomer of the corresponding 4-alkenyl product **37**.⁸⁹



2. Dilithiation reactions of 3-Arylsydnone.

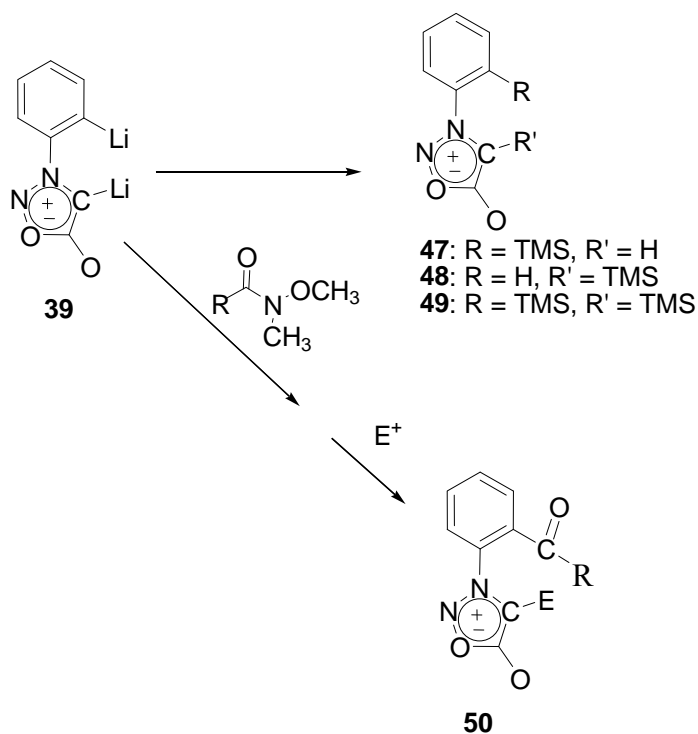
Dilithiation of 3-arylsydnone has become a recent focus of sydnone chemistry, and has been successfully achieved by Krein and Turnbull.^{79, 90-92} Initially a dilithio sydnone intermediate **39** was produced by the reaction of 3-(2-bromophenyl)-4-bromosydnone **38a** with butyllithium at -78°C. Upon treatment with ethyl acetate, a sydnoindole **40** was obtained in good yield.



Krein and Turnbull have proven the versatility of this method and successfully applied it to other esters. One undesirable drawback however, was the loss of weight going from starting material to product caused by the sacrifice of two bromine atoms. Thus; an alternative starting material had to be sought. When 3-(2-bromophenyl)sydnone (**38b**) was used instead of **38a** using similar conditions it was found that the same

transformations were achieved. On pursuing this further, Krein and Turnbull discovered that the dilithio- intermediate **39** could be prepared directly from 3-phenylsydnone **5** ($R'=Ph$, $R=H$) using N,N,N,N-tetramethylethylenediamine (TMEDA) to increase the basicity of butyllithium. This was complemented by the anticipated, apparent *ortho*- directing effect of the sydnone ring. Thus, it was possible to react at the *ortho*-aryl site without the need for metal halogen exchange. This dilithio-species was reacted with several electrophiles to yield a variety of disubstituted sydnones (cf. **39** to **41-46**). More recently the reaction has been found to produce the same results without the use of TMEDA by raising the reaction temperature from -78°C to -50°C ⁹³

With an attractive route to **39** now available, Krein and Turnbull elected to explore the idea of selective substitutions on arylsydnones. The idea stemmed from the realization that the acidity of the proton at the *ortho* aryl position is substantially different compared to that at the sydnone-4 position. The pK_a of the 4-sydnone proton is estimated to be 18-20 pK units, while the *ortho* aryl proton is estimated to have a pK of approximately 40 pK units. It was anticipated that this difference could be exploited in selective substitution reactions. The idea was tested initially by generating the di-lithio species and reacting it with one equivalent of an electrophile. When the di-lithio sydnone **39** was prepared and reacted with one equivalent of chlorotrimethylsilane, it was found to produce four products: *ortho* substituted, sydnone C-4 substituted, disubstituted and unsubstituted **47-49**, **38b** respectively. The results suggested that chlorotrimethylsilane was too strong an electrophile to permit *ortho* selection.

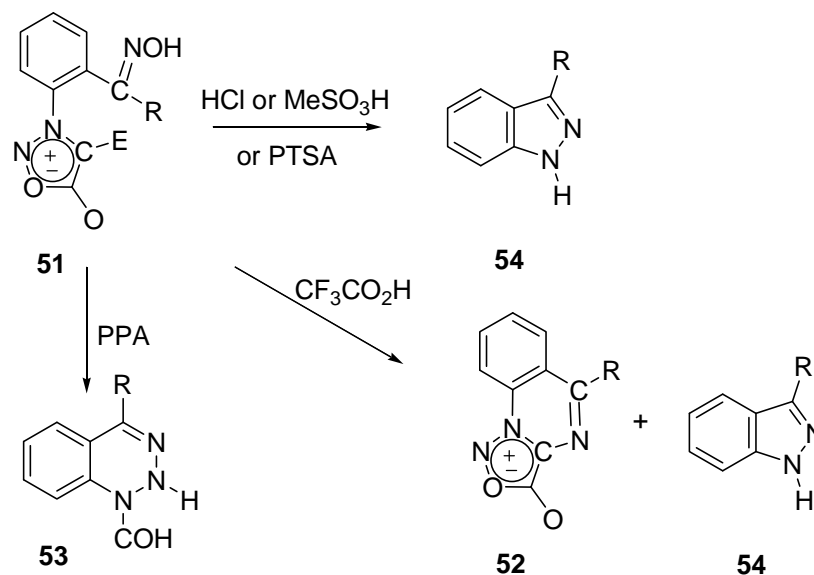


Cognizant of this possibility, Turnbull and Krein attempted the reaction with less reactive electrophiles and Weinreb's amides were chosen since they have known advantages in similar transformations. Hence, N-methoxy-N-methylbenzamide was reacted with **39** to produce the *ortho*-benzoyl species **50** ($R=Ph, E=H$) in good yield and this process was extended to the preparation of other *ortho*-acyl sydnone species **50** ($R=$ various, $E=H$). Overall, this approach provided a “one pot” synthesis of *ortho*-acyl sydnone species^{79, 90-92} from easily prepared 3-phenylsydnone. Since, after initial reaction at the *ortho*-aryl position, the sydnone anion remains, one equivalent of a second electrophile can be added to promote further functionalization at the C-4 position of the sydnone ring. This provides a route to many unsymmetrically functionalized sydnone species **50** ($R=$ various, $E=Br, I, SiR'_3$).

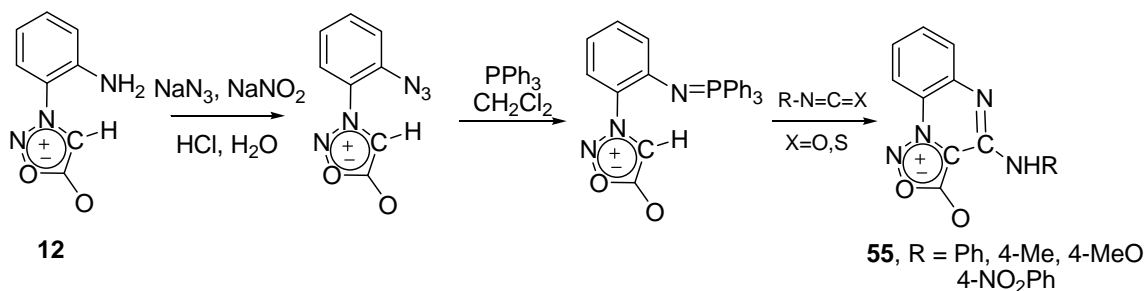
Lithiation studies⁹³ on mono and dimethoxy substituted arylsdnones, followed by trapping with electrophiles (e.g. iodine, trimethylsilyl chloride) led to the discovery that sodium borohydride could remove iodines attached to both the sydnone C-4 and the *ortho*-position of the aryl ring, whereas aqueous sodium sulfite selectively removed the iodo group from the sydnone ring. In addition, selective desilylations of disilylsydnones were achieved using potassium carbonate or tetrabutylammonium fluoride.

3. Reactions of *ortho* substituted aryl sydnones.

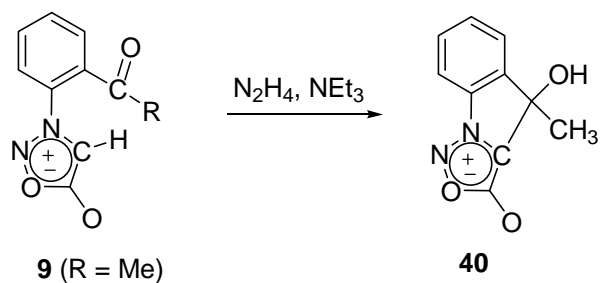
Oximosydnones are potential precursors of fused ring sydnones. Turnbull and Saljoughian reported⁹⁴ that by treating oximosydnones **51** (R=Me or Et) with any one of a variety of acids it was possible to obtain the corresponding sydnquinazoline **52**, benzotriazine **53** or indazole **54** depending on which acid was used.



Structural isomers of the sydnocarbonyl **52**, viz 4-(arylamino) sydnocarbonyl **55**, have been prepared in good to excellent yield (60-90%) by aza-Wittig carbodiimide formation followed by intramolecular electrophilic cyclization.⁹⁵

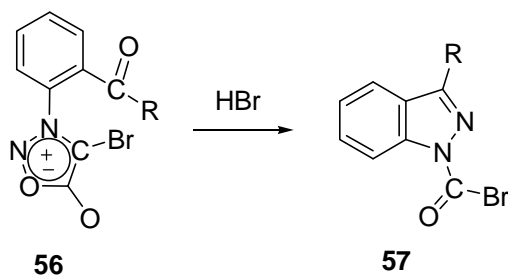


Two serendipitous discoveries have resulted in the preparation of fused-ring sydnocarbonyl **40** and various bromocarbonyl indazoles **57**. It was found that by treating 3-(2-acetylphenyl)sydnocarbonyl (**9**, R=Me) with hydrazine under basic conditions, the major isolable product was the fused ring sydnocarbonyl **40** and not the anticipated hydrazone derivative.⁹⁶

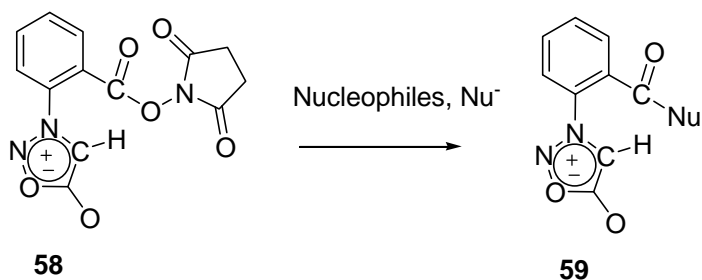


To extend this work further, it was considered of interest to place a bromo-leaving group on the acetyl methyl. Accordingly, 3-(2-acetylphenyl)-4-bromosydnocarbonyl **56** (R=Me) was treated with Br₂/hν or CuBr₂. Surprisingly the bromocarbonylindazole **57** (R=Me) was obtained rather than the expected sydnocarbonyl **56** (R=CH₂Br). It was thought that the transformation resulted from the formation of HBr *in situ* and, indeed, when various 4-

bromo *ortho*-acyl sydnone (cf. **56**) were subjected to a stream of HBr gas the corresponding bromocarbonylindazoles **57** were formed in good yield (60-85%).⁹⁷



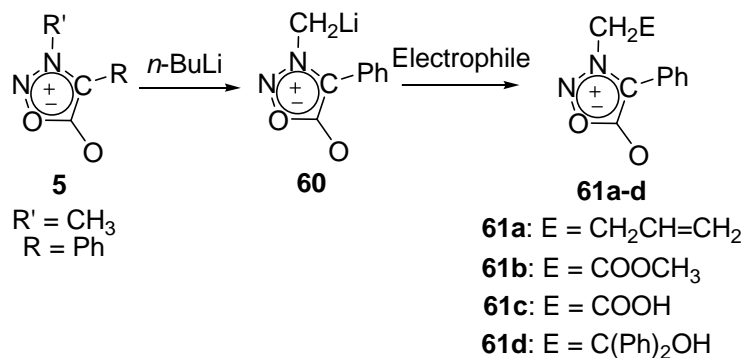
One obstacle to the study of the reactions shown above has been that sydnone with an *ortho*-carbonyl substitution are relatively hard to come by; they often must be made in several steps starting from the appropriate aniline derivative. Recent work has shown that a variety of *ortho*-acylarylsydnone can be prepared from one or two intermediates by reacting nucleophiles with activated *ortho*-carbonyl species.⁹⁸ For example, 3-[2-(succinimido)oxycarbonyl] phenyl] sydnone (**58**) was reacted with twelve different nucleophiles to afford the corresponding *ortho*-arylacylsydnone **59** in yields ranging from 23%-63%.



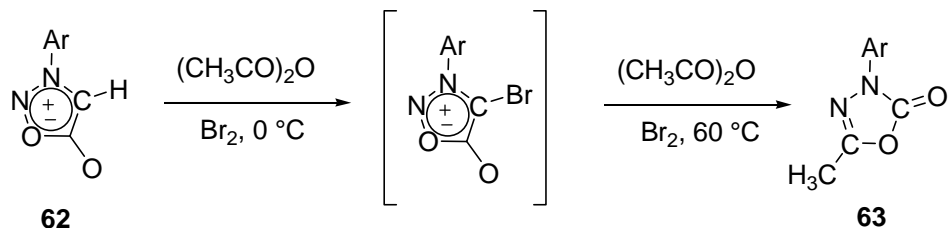
4. Miscellaneous, recent reactions of sydnones.

Recently, from 1996 to 2009, some new chemistry has been reported with sydnones.

Kalinin and Cherepanov have explored metallation of 3-methyl-4-phenylsydnone (**5**) ($R=Ph$, $R'=CH_3$).⁹⁹ In their study it was found that a proton could be abstracted from the methyl group of **5** with butyl lithium at $-90^\circ C$ to form the rather unstable lithio-intermediate **60**. Subsequent reactions with a variety of electrophiles led to several functionalized sydnones **61** (12% to 70% yield) through a common intermediate.

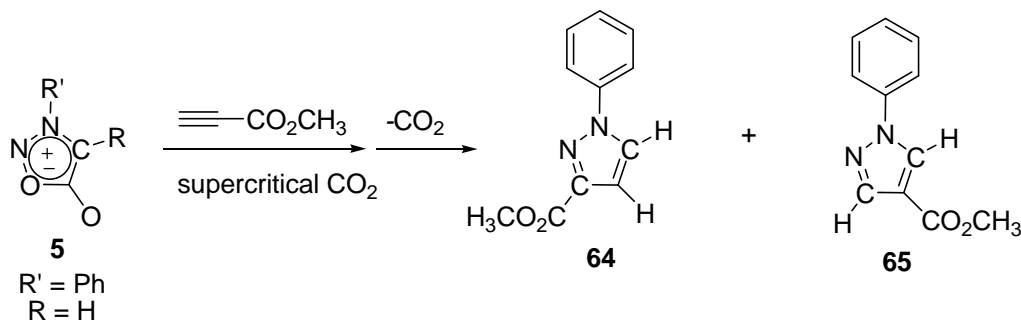


Mallur, Bharat and Badami⁵⁹ recently used sydnones as intermediates to 3-aryl-5-methyl-1,3,4-oxadiazolin-2-ones **63**. Their intention was to synthesize such species and test them for antimicrobial activity. The desired 3-aryl-5-methyl-1,3,4-oxadiazolin-2-ones **63** were prepared from 3-arylsydnones **62** by reaction with bromine in acetic anhydride as illustrated with a general example below.



According to their proposed mechanism, the reaction involves initial sydnone bromination to form a 4-bromo intermediate that is not isolated followed, at increased temperature, by 1, 3-dipolar cycloaddition between the 4-bromosydnone and acetic anhydride. Considering the fact that no attempt was made to remove HBr formed as a by-product, and the unprecedented nature of the suggested cycloaddition, this mechanism seems suspect. The transformation is useful however, and overall twenty four oxadiazolinones were prepared in yields of 70-90%, most of which showed antibacterial and antifungal activity.

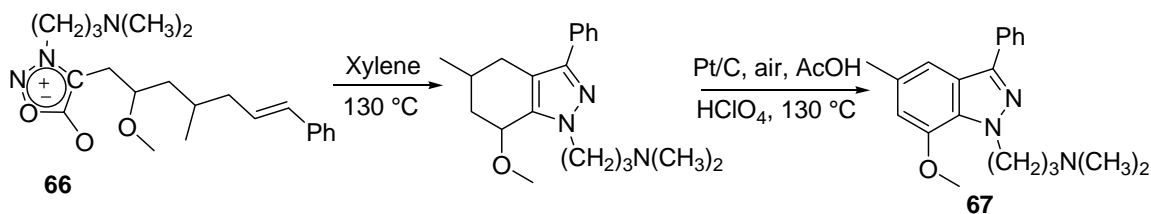
An additional, transformation exploiting the ability of a sydnone to participate in 1,3-cycloadditions was carried out by Turnbull, McGowin and Totoe. Their research involved a known sydnone reaction, *viz.* the reaction of 3-phenylsydnone, **5** ($\text{R}=\text{H}$, $\text{R}'=\text{Ph}$) with methyl propiolate, in supercritical carbon dioxide.¹⁰⁰



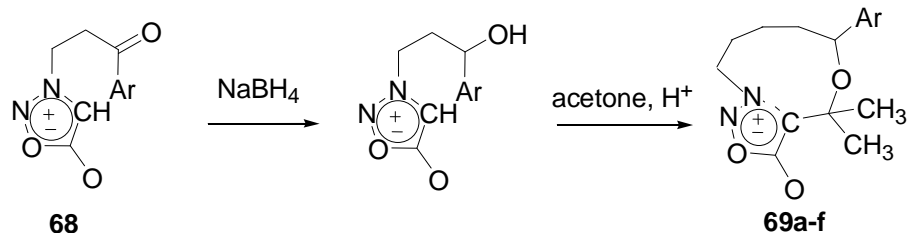
In this reaction, two regioisomers (**64** and **65**) are formed due to methyl propiolate being unsymmetrical. The temperature in the supercritical fluid reactor was varied, as well as

pressure, to see if this had an effect on reaction selectivity. Generally, it was found that increasing reaction temperature decreased reaction selectivity, while increasing reaction pressure increased reaction selectivity. Thus the reaction in supercritical carbon dioxide provided a selectivity advantage over running the reactions under standard conditions (toluene, heat). Another advantage is that the reaction is carried out in a “green” solvent (carbon dioxide versus toluene).

As another example of a sydnone being used in synthesis, Yeu et al. used **66** in an expedient synthetic route to the antidepressant 1-[3-(dimethylamino)propyl-5-methyl-3-phenyl-1H-indazole (**67**).¹⁰¹ This synthesis involved an *intramolecular* 1,3-dipolar cycloaddition reaction of **66** followed by aromatization to obtain the desired product.

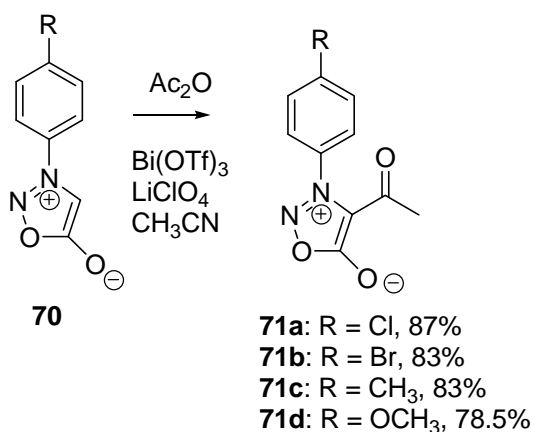


Zhang, Wu and Yin have prepared novel fused ring sydnone containing a seven membered ring fusion.¹⁰³ Their synthetic route involved the reduction of 3-arylethylsydnone **68** with sodium borohydride to obtain 3-(aryl-3-hydroxypropyl)sydnone. Subsequent treatment of these species with acetone and concentrated sulfuric acid or boron trifluoride etherate produced the corresponding fused ring sydnone **69a-f** in 60% to 85% yield.



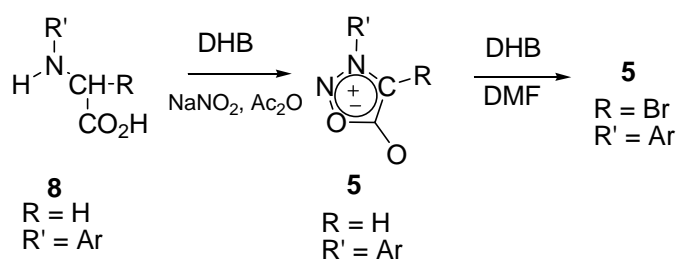
Ar = a) C_6H_5 ; b) $4\text{-CH}_3\text{C}_6\text{H}_4$; c) $4\text{-ClC}_6\text{H}_4$; d) $4\text{-BrC}_6\text{H}_4$; f) 2-naphthyl

Friedel-Crafts acylations on the 4-position of the sydnone ring have been achieved using various alkyl anhydrides (mainly acetic anhydride), bismuth triflate and lithium perchlorate in anhydrous acetonitrile at 95°C (**70** to **71a-d**).²³ The advantages to this approach over the numerous previously reported syntheses are that the anhydride need not be used as solvent and less than stoichiometric quantities of the reagents can be employed. Several attempts were made to extend this study to the preparation of diacyl sydnone (substitution also at the *ortho*- position of the aryl ring) using the strongly activated sydnone 3-(3,5-dimethoxyphenyl)sydnone **15** ($\text{R} = 3,5\text{-MeO}$) but no method so far has given only the desired diacyl product.



Finally, it has been reported recently¹⁰⁴ that 1,3-dibromo-5,5-dimethylhydantoin (DBH) in combination with NaNO_2 and acetic anhydride efficiently catalyzes the one-pot

conversion of various N-arylglycines ($R'=Ar$) to arylsydnones **5** ($R=H$, $R'=Ar$) in high yields (80-94%) under mild and neutral conditions. The advantage of this procedure is that it eliminates one step from the usual method and avoids handling of suspected carcinogens (nitrosated glycines). It was also shown that DBH can conveniently promote the bromination of these sydnones to their 4-bromo substituted congeners ($R=Br$, $R'=Ar$) in excellent yields in DMF at room temperature.



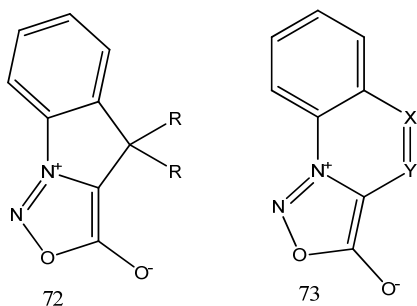
Background to the current Research

1. Arylsydnone Ring Fusion.

Recently, fused ring arylsydnones have stimulated interest since the ring fusion is a route to interesting new compounds that may possess useful biological activity. Fused ring sydnones of interest can be placed into two categories: one in which the fusion occurs through a single carbon bridge adjacent to the sydnone ring (cf.**72**) and another in which the fusion occurs through an unsaturated two-atom bridge (cf.**73**). It is thought that the ring fusion inherent in these two species may facilitate the *in vivo* metabolism of the sydnone ring and in the process generate yet to be observed biological benefits. In

addition, sydnones have also been used to generate potentially useful non-sydnone heterocycles such as benzotriazines and indazoles.

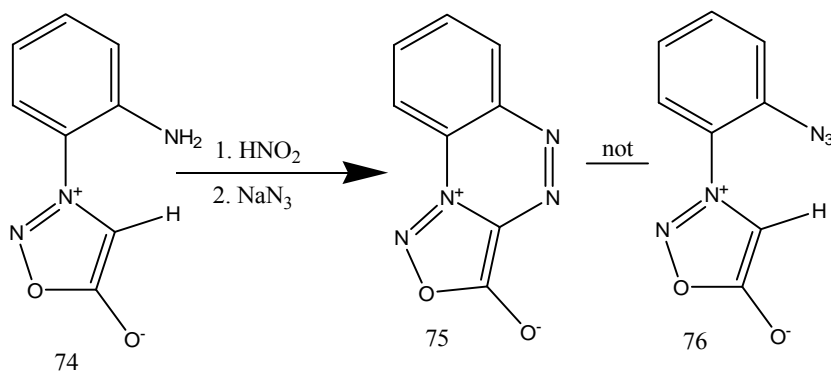
Scheme 1



This section attempts to elaborate on ideas previously discussed in the introduction so as to provide the reader with some background information that will clarify the rationale for the current work, and how it might lead to fused ring arylsydnones.

In 1977, Preston and Turnbull¹⁰⁶ treated 3-(2-aminophenyl) sydnone (**74**) with nitrous acid followed by sodium azide in an attempt to synthesize azidosydnone **76**. Surprisingly, the product was the fused ring benzotriazine **75**.

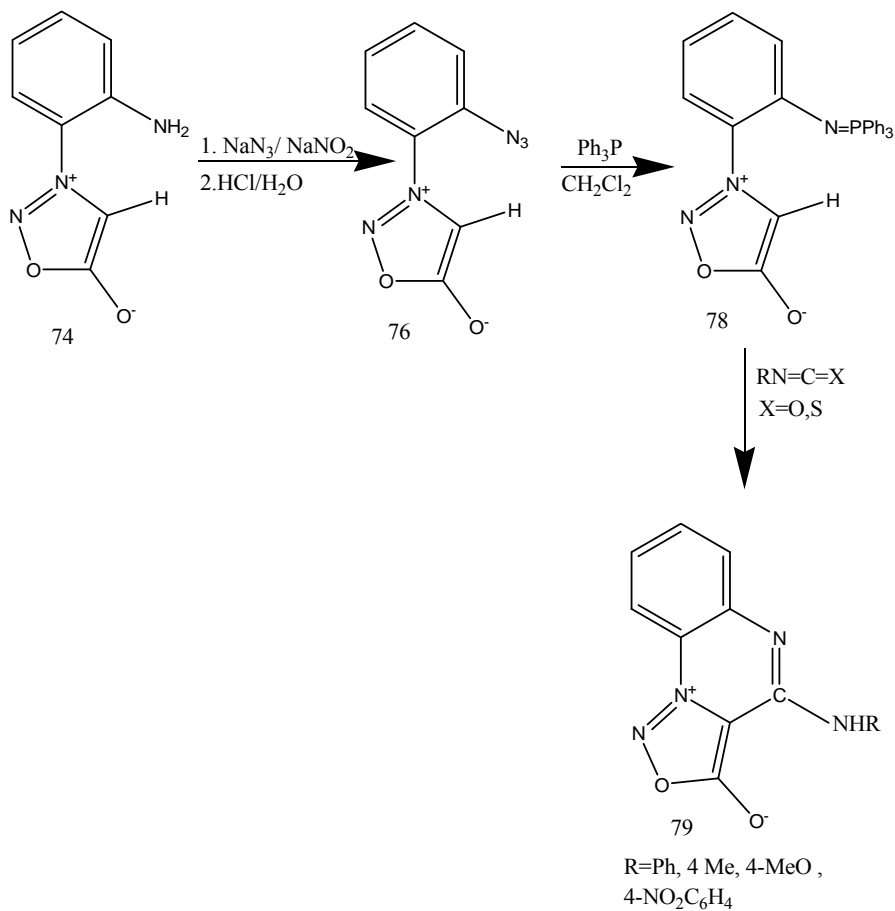
Scheme 2



Since the sydnone ring undergoes electrophilic aromatic substitution, it was thought that the fused ring sydnone was formed by an intramolecular trapping of the intermediate diazonium species by the sydnone ring.

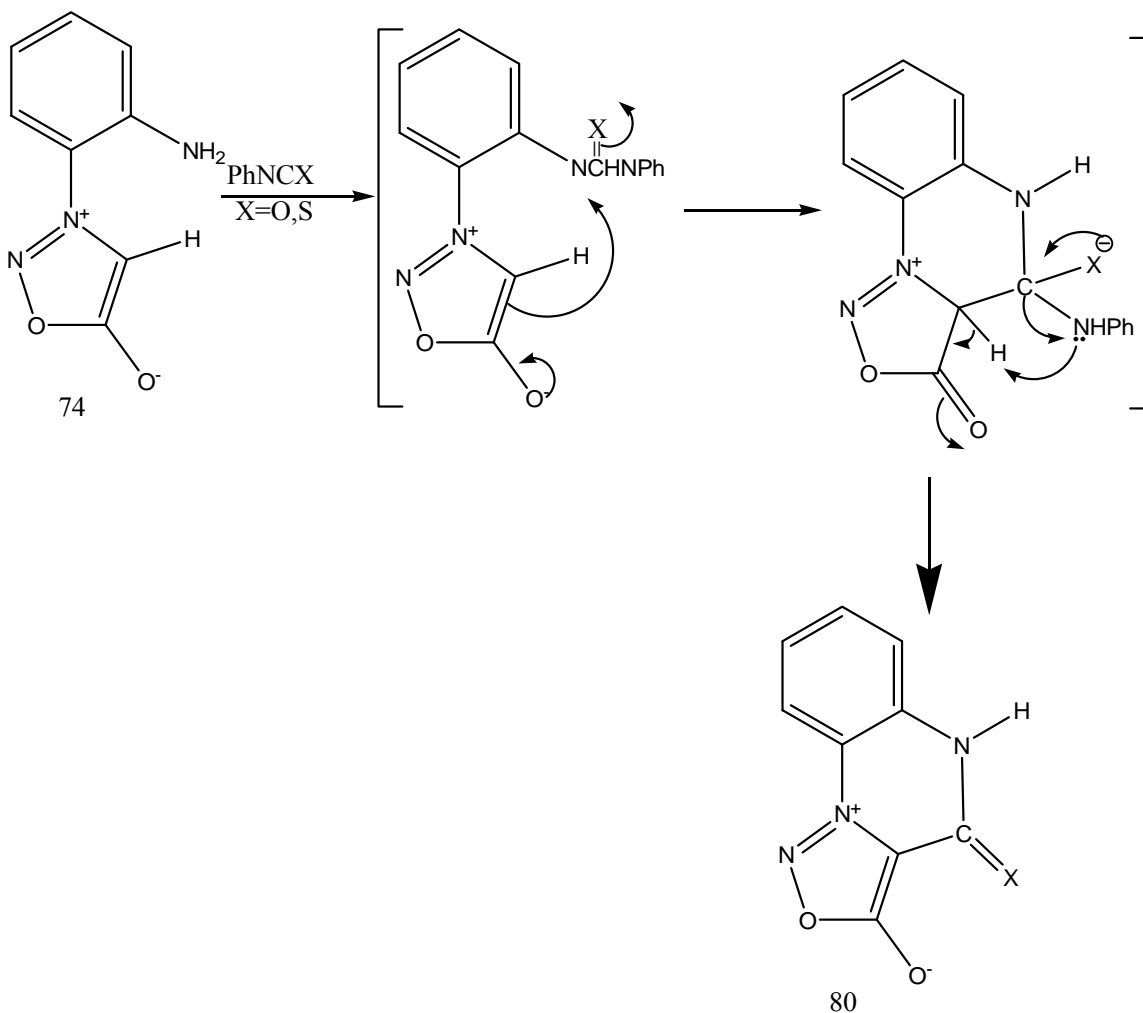
More recently (1991), Burson, Turnbull⁹⁵ and coworkers reexamined the preparative route to the azidosydnone **76**. Therein, they assumed that the trapping of the intermediate diazonium species was a competitive process and accordingly if the later were formed in the presence of an excess of azide ion, the azidosydnone **76** might result. Indeed when the aminosydnone **74** was diazotized in the presence of sodium azide **76** was formed in moderate yield. Smooth conversion to the iminophosphorane **78** was effected with triphenylphosphine and the former reacted with iso- or isothiocyanates to afford fused-ring amino sydnosquinoxalines **79** in good yields. The method of synthesis involved aza-Wittig carbodiimide formation followed by intramolecular electrophilic aromatic substitution by the sydnone ring. Yields of 60-90% were obtained. It is clear in this case again that ring fusion is achieved by generating an electrophile in close proximity to the sydnone ring.

Scheme 3



Finally, in 1994, Chan and coworkers¹¹⁶ reported a route to fused-ring sydnosquinoxalines **80** involving the addition of an isocyanate or isothiocyanate to the amino nitrogen of 3-(2-aminophenyl) sydnone (**74**). Subsequent heating effected cyclization to **80**, again by intramolecular electrophilic substitution.

Scheme 4

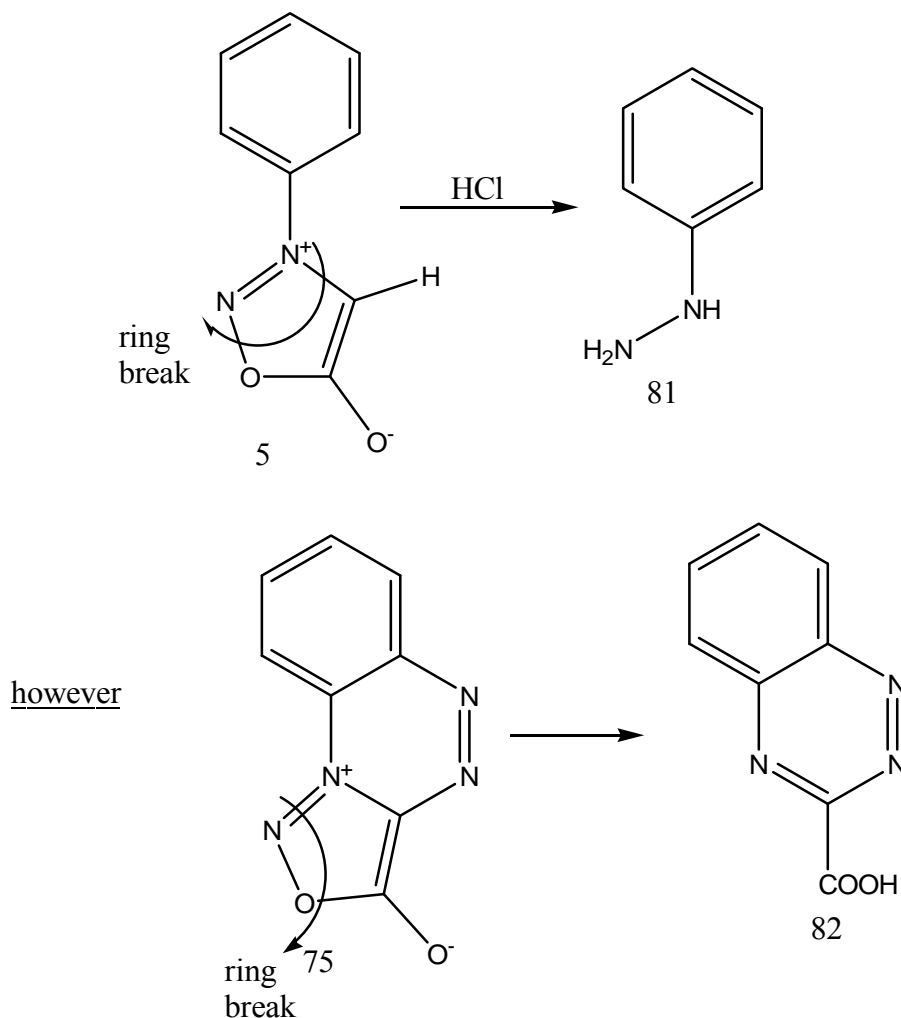


The four preceding examples illustrate the standard synthetic route to sydnone ring fusion, by creating an electrophilic center *ortho* to the sydnone ring for the sydnone to attack.

There is substantial evidence to justify the speculation that ring fusion in sydnones modulates the properties of the sydnone ring, especially with regards to where the ring will undergo hydrolytic cleavage in basic or acidic conditions.

It is known, for instance, that 3-phenylsydnone **5** ($R=H$, $R'=Ph$) undergoes acidic hydrolytic cleavage²⁴ to form N-phenylhydrazine **81**. However, hydrolysis of the fused species **75** cleaves the sydnone between the 2-3 and 1-5 bonds instead of between the 1-2 and 3-4 bonds, yielding a benzotriazine carboxylic acid **82**.

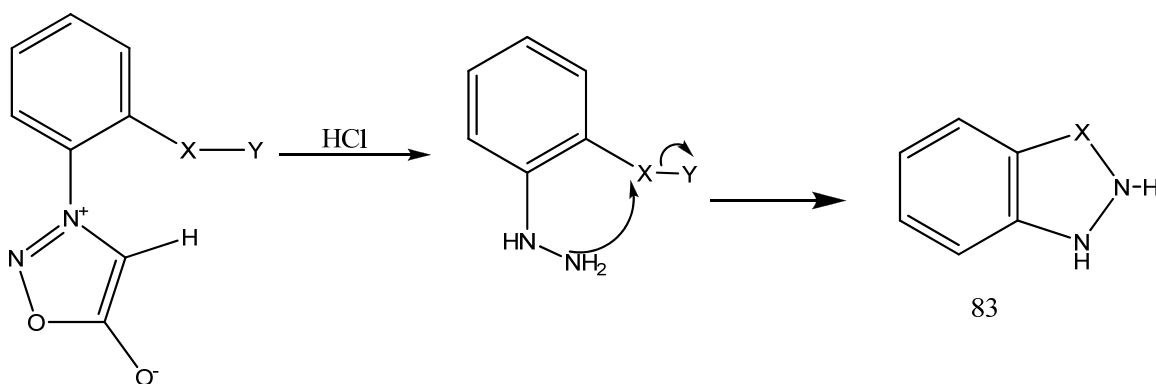
Scheme 5



This change in the way the sydnone ring breaks is of interest because it appears that the species nitric oxide is released, which is known to be an anti-hypertensive *in vivo*. This makes variants of fused-ring sydnone **75** of special interest for pharmaceutical purposes.

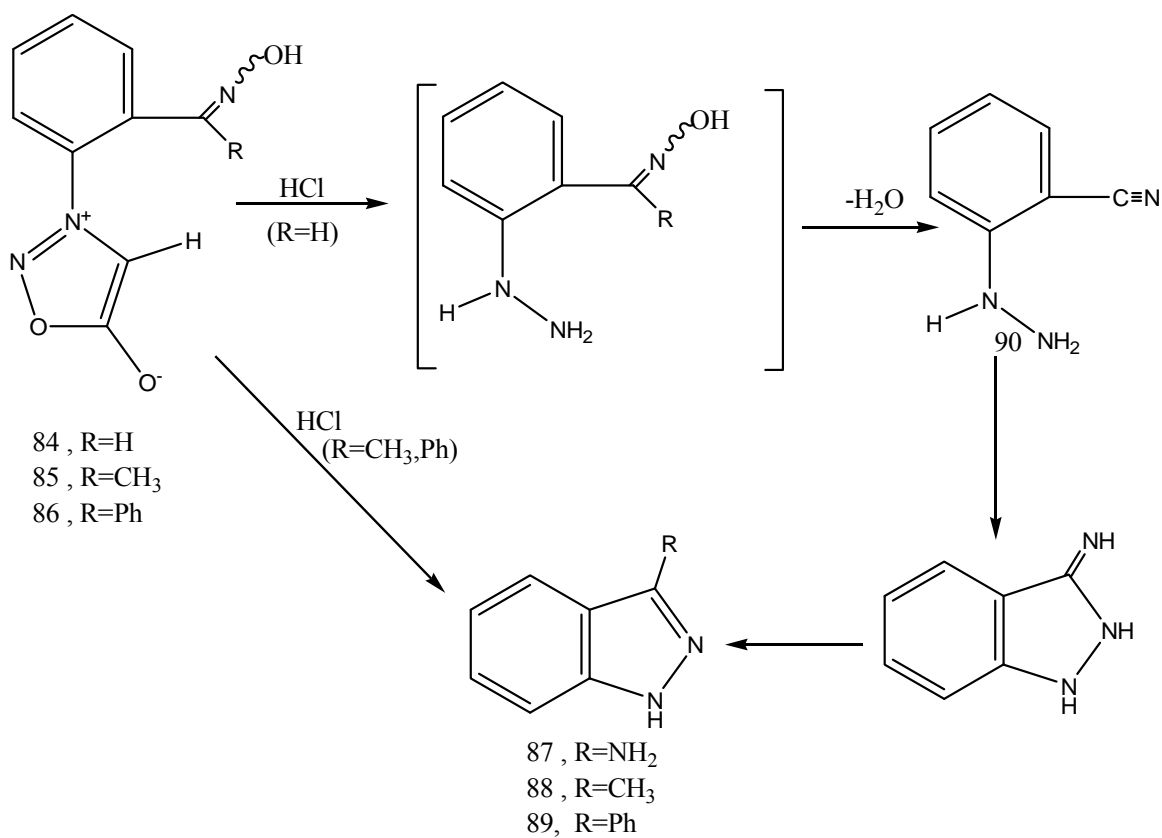
As shown in Scheme 5, under non-fused circumstances, acid cleavage of the sydnone ring gives rise to an aryl hydrazine, a powerful, nucleophilic species that can be useful for heterocyclic synthesis. It was postulated, and demonstrated, that an *ortho*-substituted arylhydrazine generated from an appropriate arylsydnone could lead to unique heterocycles (cf. **83**) upon cleavage of the latter with HCl.⁹⁶ (Scheme 6).

Scheme 6



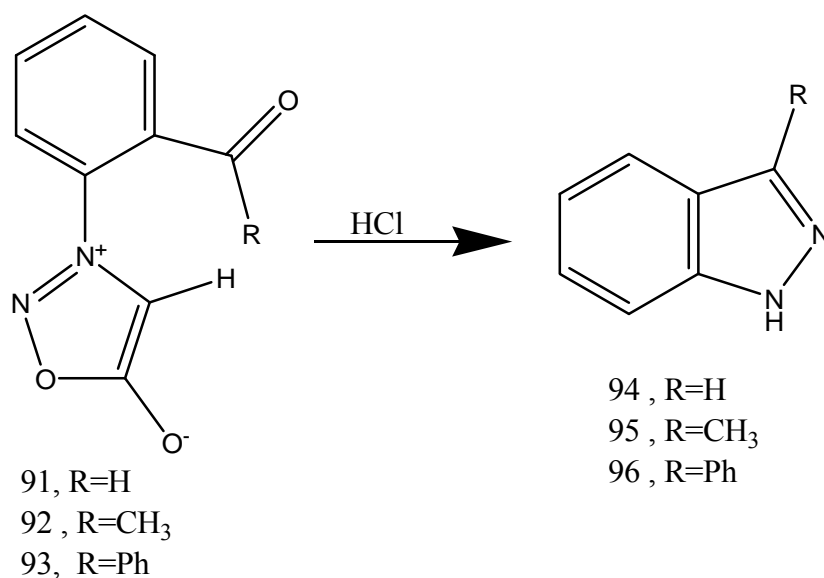
Initially, the focus of this work was to prepare indazoles from *ortho*-oximosydnone. Thus, when aldoxime **84** was treated with aqueous HCl, aminoindazole **87** was produced. It was thought that the cyclization occurred *via* a nitrile intermediate **90**. This was supported by the observation that if 3-(2-cyanophenyl)sydnone was treated with HCl the same aminoindazole **87** was formed. Ketoxiimines **85** and **86**, gave the corresponding 3-substituted indazoles **88** and **89** when treated with HCl, presumably by means of hydrazine formation and subsequent cyclization with the elimination of hydroxylamine (Scheme 7).

Scheme 7



In addition, similar conditions were applied to the aldehydes **91** or ketones **92** and **93** to give the corresponding indazoles (Scheme 8).

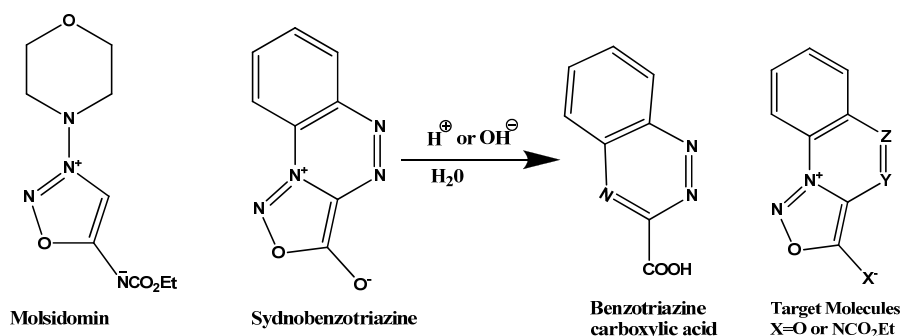
Scheme 8



Aims of the Present Work

The main focus of this research was to explore routes leading to the synthesis of functionalized fused-ring sydnoquinolines. Earlier work by Turnbull and Preston in 1977 had revealed that a sydnobenzotriazine, a fused-ring sydnone, could undergo acid hydrolytic cleavage to yield a benzotriazine carboxylic acid.¹⁰⁶ This unusual mode of cleavage (as compared to non-fused sydnone congeners) is thought to arise due to the aromatic nature of the benzotriazine by-product and is coupled with the release of nitric oxide (NO) or an NO congener. NO is an important species, since it facilitates several important processes in the body. One of its important roles is its mediation in the physiological process of vasodilation with consequent lowering of blood pressure. Molsidomin (an effective hypotensive drug) is a sydnone analog which is known to exert

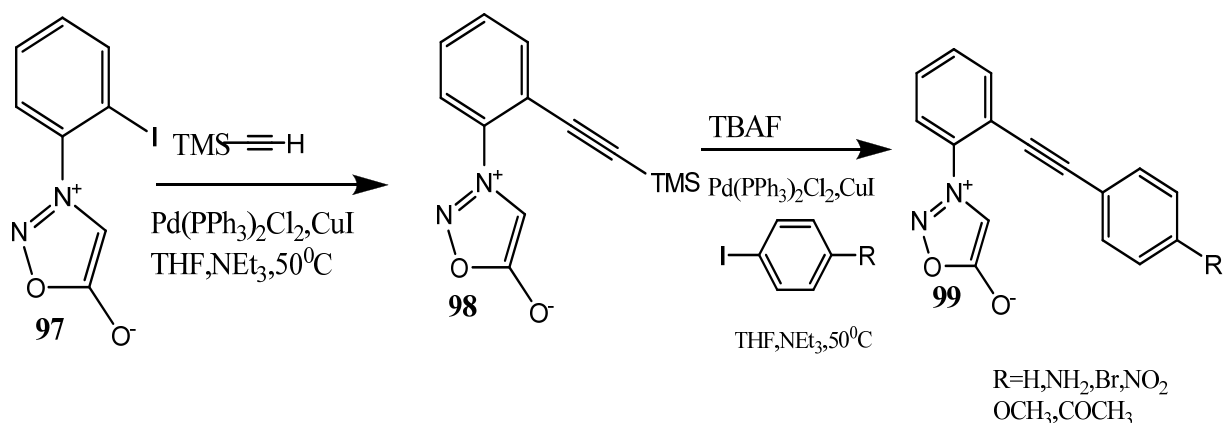
its effect by release of NO due to enzymatic activation. It has been of interest therefore to prepare fused ring sydnones analogous to sydnobenzotriazine as potential NO prodrugs.



Previously, in our laboratory, Weisner had shown that *ortho*-iodinated sydnones, especially in the form of 3-(2-iodophenyl)sydnone (**97**), could be used to synthesize a variety of *ortho*-alkynyl sydnones²², which in turn could potentially be converted to novel fused-ring sydnones (sydnoquinolines). He went on to synthesize the versatile intermediate, 3-(2-trimethylsilylethynyl)phenyl)sydnone (**98**), in good yield by the coupling of 3-(2-iodophenyl)sydnone (**97**) with trimethylsilylacetylene under Sonogashira conditions.

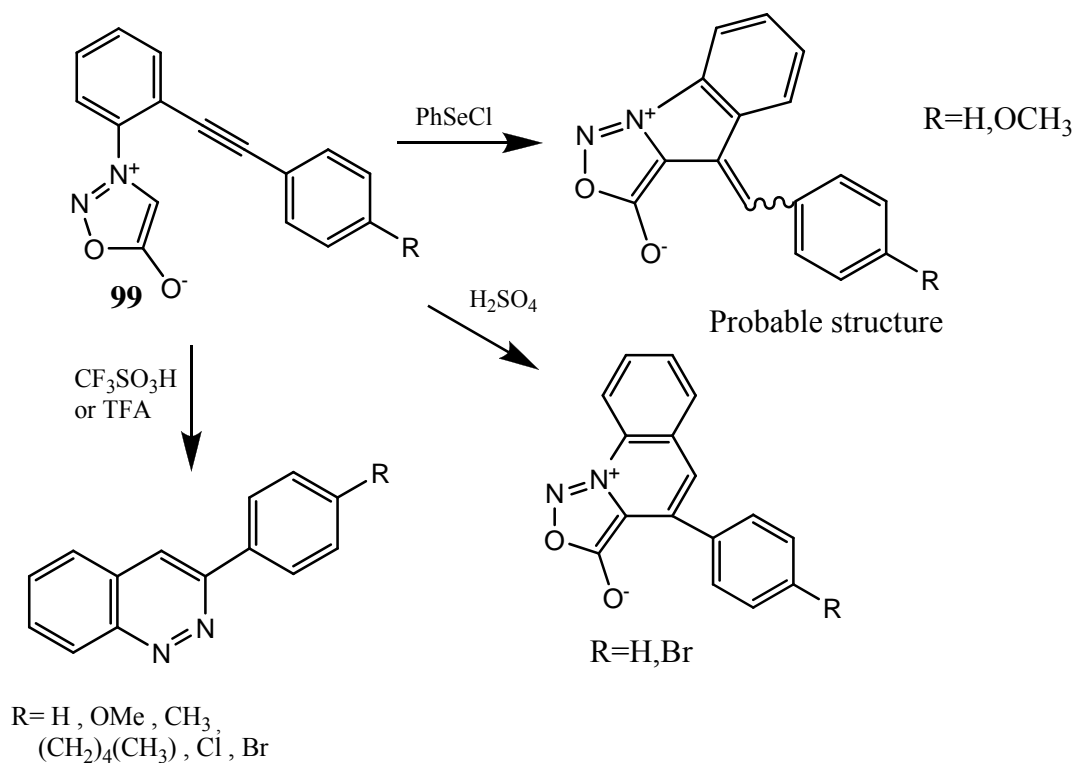
Using this intermediate **98**, several *ortho*-alkynyl sydnones **99** were prepared *via* one-pot desilylation with tetrabutylammonium fluoride and Sonogashira coupling with *para*-substituted aryl iodides as shown in Scheme 9. In addition, a three-reaction-in-one-pot procedure was developed to access some of these species directly from 3-(2-iodophenyl)sydnone (**97**).

Scheme 9



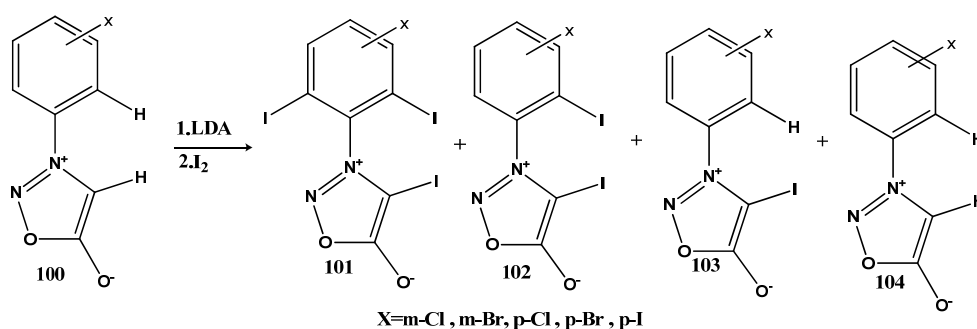
The reaction of **99** with electrophiles was tested as a potential avenue to novel fused-ring sydnones. As had been anticipated, it was evident that the electrophile, phenylselenenyl chloride, induced cyclization of 3-(2-phenylethynyl)phenylsydnone **99** ($\text{R}=\text{H}$) and 3-(2-(4-methoxyphenylethynyl)phenylsydnone **99** ($\text{R}=\text{OMe}$) in moderate yield. Although the identities of the resulting fused-ring compounds are still to be fully elucidated, it is likely that they are novel sydnoindoles (Scheme 10). However, the cyclization of 3-(2-(phenylethynyl)phenylsydnone **99** ($\text{R}=\text{H}$) and 3-(2-(4-bromophenylethynyl)phenylsydnone **99** ($\text{R}=\text{Br}$) to the corresponding sydnoquinolines using concentrated sulfuric acid was more conclusive, albeit resulting in a very low yield of fused-ring product. When trifluoroacetic acid and trifluoromethanesulfonic acid were employed in this transformation the alkynyl species **99** were converted to novel cinnolines, presumably *via* sydnone ring cleavage to the corresponding monosubstituted hydrazine, followed by acid-induced cyclization. Scheme 10 is a summary to depict the series of reactions aforementioned.

Scheme 10

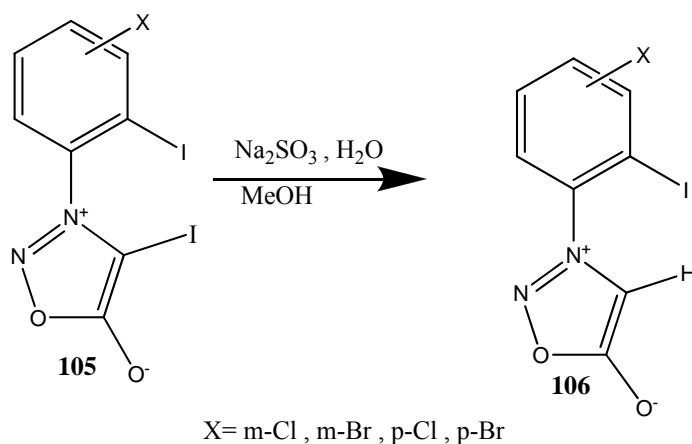


Following on Weisner's work, Dossa synthesized *ortho*-alkynyl sydrones as precursors to functionalized sydnosquinolines.¹⁰⁷ In his work, the versatile intermediates, 3-(4-halo-2-iodophenyl)sydrones and 3-(3-halo-2-iodophenyl)sydrones **106** were synthesized in modest yields using a sequence involving dilithiation of 3-(4-halophenyl)-sydrones and 3-(3-halophenyl)sydrones with the strong bases butyl lithium or lithium diisopropylamide, trapping the intermediate dianions with iodine, and removing the iodine at the C-4 position as shown in Schemes 11 and 12.

Scheme 11



Scheme 12



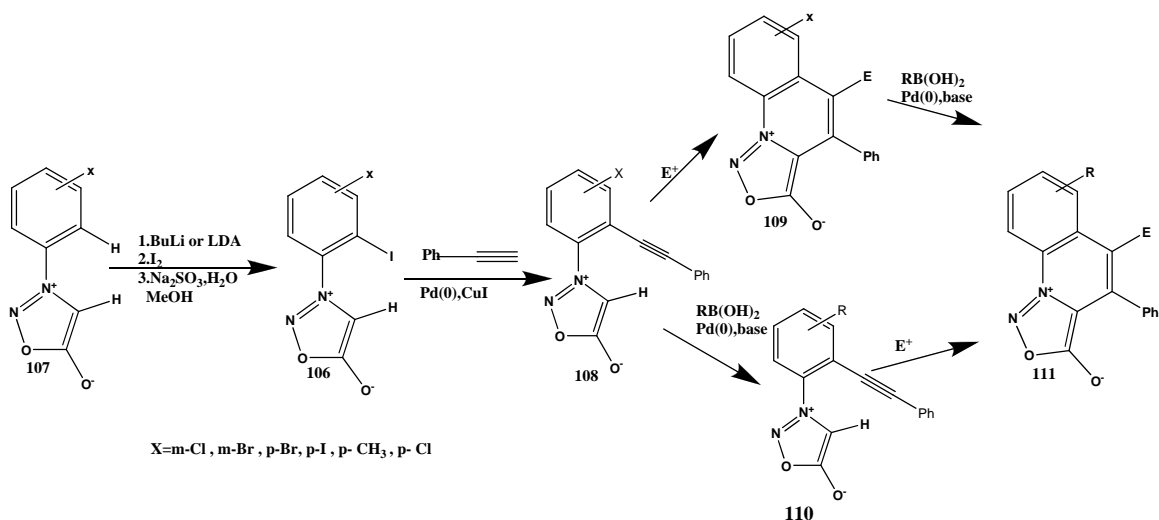
It is worthwhile to note though, that while the desired *ortho*-iodophenyl syndnones **106** could be prepared as outlined in schemes 11 and 12, the separation of the products proved to be tedious and difficult. Moreover, of the four species isolated in the lithiation process (see Scheme 11), no *ortho*-iodophenyl syndnones were isolated directly and, accordingly, the latter had to be synthesized in a second reaction, resulting in an even lower overall yield.

Cognizant of these disparities between the quantities of input materials used and those obtained for the putative products sought, it was thought that another efficient alternative

method that was less time consuming and made use of less material would be worthwhile to explore. Thus, one objective of the present work was to review the old methodology used in an attempt to improve overall yields as well as explore new synthetic strategies and improve efficiency. Once the *ortho*-iodophenyl sydnones **106** could be synthesized in satisfactory yields, then that would open avenues for the synthesis of sydnoquinolines **110** in sufficient yields through *ortho*-alkynyl compounds **109** and their further functionalization. Since sydnones display significant biological properties it can be assumed that further functionalization of the sydnoquinolines **110** and their precursors will yield other biologically interesting molecules. In previous attempts it is notable that although sydnoquinolines were presumed to have been produced ultimately, insufficient yields hindered their full characterization and elucidation.

With this overall premise, the leading hypothesis was that if the intermediate 3-(3-halo-2-iodo)phenyl)sydnones and 3-(4-halo-2-iodo)phenyl)sydnones **106** could be synthesized efficiently by dilithiation of the corresponding 3-(3-halophenyl)sydnones and 3-(4-halophenyl)sydnones **105** using *n*-butyllithium, trapping with iodine, followed by removal of the iodine at the 4-position with aqueous sodium sulfite then, by induction, better overall yields of *ortho*-alkynyl phenyl sydnones **109** as well as sydnoquinolines **110** would be attainable (Scheme 13).

Scheme 13



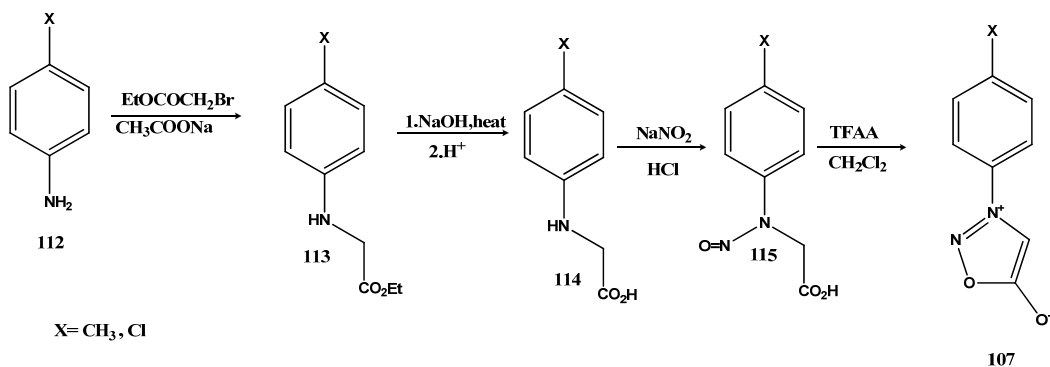
The intermediate *ortho*-iodophenyl sydnone such as **106** are very crucial in these transformations. As shown in Scheme 13, coupling of **106** with phenyl acetylene under Sonogashira conditions should lead to a selection of *ortho*-alkynyl phenyl sydnone **108**. In principle, these should then be cyclized to yield the fused ring systems **110**. Later modifications of these may then afford **111**. Another alternative pathway would involve prior coupling reactions at the 3' or 4'-positions of **108** to afford various *ortho*-(phenylethynyl)phenyl sydnone **110** which, upon reaction with electrophiles, could provide the same novel sydnoquinolines **111**.

Discussion

As stated in the Aims section, the main thrust of this work was to review and explore efficient ways to synthesize the key sydnone intermediates for Sonogashira coupling reactions, namely *ortho*-iodophenyl sydnones **106**, especially those derived from 3-(4-chlorophenyl) sydnone (**107**, X= para-Cl) and 3-(4-tolyl)sydnone (**107**, X= para CH₃).

However, the entry point had to be the synthesis of the appropriate starting sydnones **107** from the appropriate anilines **112**. The later were chosen intentionally to test the appropriateness of methods for both situations in which an electron donating species (methyl) or an electron withdrawing species (chlorine) are attached to the 4-position of the aryl group. The sydnones **107** were synthesized using a four-step approach with little or no purification until the last step, where the desired sydnone was purified by either column chromatography or recrystallization. The stepwise approach involved: (1) alkylation of the appropriate aniline **112** with ethyl bromoacetate and sodium bicarbonate in ethanol to yield the glycine ester **113**; (2) hydrolysis of the ester with sodium hydroxide to reveal the N-arylglycine **114** ; (3) nitrosation of the glycine with sodium nitrite in hydrochloric acid and water to provide the nitroso compound **115** ; and (4) cyclization of the nitrosated glycine to the sydnone with trifluoroacetic anhydride (TFAA) in dichloromethane or with acetic anhydride (Scheme 14).

Scheme 14



To confirm the identities of products comparisons were made (IR, TLC, and m.p) with the authentic products previously synthesized in our laboratory. Comparison of **112**, **113** and **114** by TLC (SiO₂,CH₂Cl₂ as eluent) did show differences in polarity suggesting that the compounds are different. The infra red spectrum for **114** (X=CH₃) showed the expected amino acid OH stretch from 3021cm⁻¹ to 2701cm⁻¹. The same amino acid OH stretch was visible in the spectrum for **114** (X=Cl) ranging from 3075cm⁻¹ to 2530cm⁻¹. A notable difference was the presence of a strong sharp peak at 3415cm⁻¹ (presumably NH stretch) in the infra red spectrum for **114** (X=Cl) which was absent in the spectrum of **114** (X=CH₃), and the relatively complex nature of the fingerprint region in **114** (X=Cl) as compared to that for **114** (X=CH₃). The general route (Scheme 14) afforded the glycines **114** in yields ranging from 30% to 96% for both glycines, and **107** in yields ranging from 14.5% to 66% for both arylsydnone. A comparison of **114**, **115** and **107** by TLC (SiO₂,CH₂Cl₂ as eluent) also showed differences in polarity, again suggesting the compounds were different. The infra red spectrum of **115** was not obtained since the

compound is a suspected carcinogen, thus all handling and processing of the compound was done carefully in the fume hood with adequate protective clothing. The infra red spectra for **107** showed the characteristic sydnone carbonyl peaks at 1756.44cm^{-1} ($\text{X}=\text{CH}_3$) and 1733.70cm^{-1} ($\text{X}=\text{Cl}$) as well as the sydnone C-H stretch at 3138.63cm^{-1} ($\text{X}=\text{CH}_3$) and 3112.56cm^{-1} ($\text{X}=\text{Cl}$). The target compounds were also characterized by NMR. Each ^1H NMR spectrum (for **107** ($\text{X}=\text{CH}_3, \text{Cl}$)) displayed the expected doublet of doublets pattern in the aromatic region as well as the sydnone proton singlet at chemical shift 6.8 ppm with an integral ratio of 4:1. The ^1H NMR spectrum for **107** ($\text{X}=\text{CH}_3$) showed also a singlet at 2.65 ppm confirming the presence of the methyl group. The ^{13}C -NMR spectra for **107** ($\text{X}=\text{CH}_3, \text{Cl}$), revealed, as expected, two taller peaks indicative of the two sets of aromatic C-H in the aryl ring, four smaller signals indicative of the quaternary carbons present on the aromatic ring and the two sydnone carbonyl peaks at ~ 168 . ppm. The use of acetic anhydride proved to be unsatisfactory for the production of 3-(4-chlorophenyl) sydnone (**107**, $\text{X}=\text{Cl}$) since the resulting product was difficult to purify. However, the use of acetic anhydride proved to be much more effective for the synthesis of the *para*-tolyl sydnone **107** ($\text{X}=\text{CH}_3$) resulting in modest yields of pure material (45-50%), which could be used without further purification. Even given the modest yields, since large quantities of starting materials were required, the use of acetic anhydride was the method of choice owing to the prohibitive costs of trifluoroacetic anhydride. In contrast, when time was of the essence, trifluoroacetic anhydride was the reagent of choice to generate reasonable quantities of starting material.

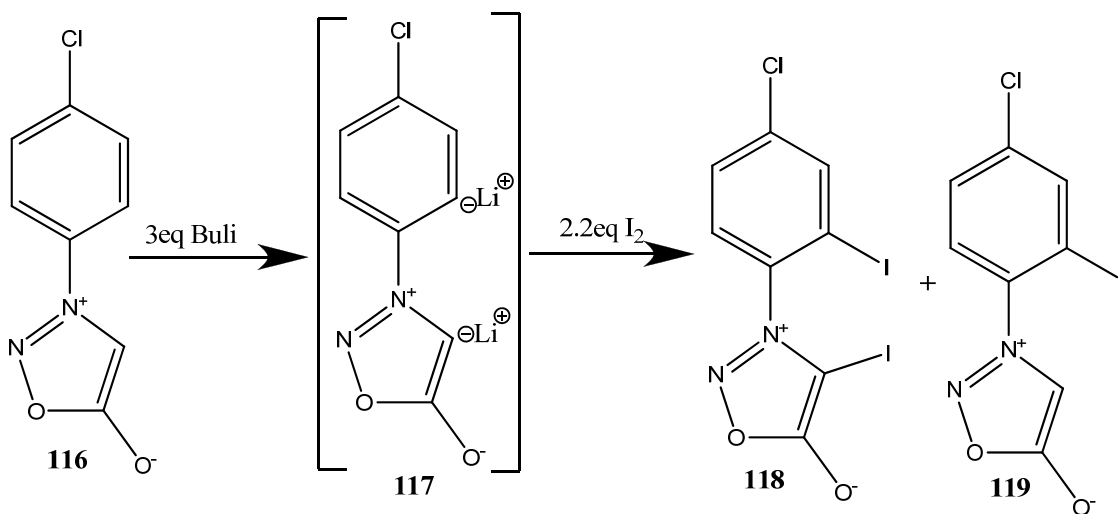
1. Iodination of arylsydnones **116** and **120** using lithiation techniques.

Previous work from several sources has revealed that the sydnone ring can act as an *ortho*-director of lithiation upon treatment of an aryl sydnone with a strong lithium base such as lithium diisopropylamide (LDA) or *n*-butyllithium. Subsequent reaction with an electrophile such as iodine or chlorotrimethylsilane allows the placement of the electrophile either at the 4-position of the sydnone ring and the *ortho*-position of the aryl ring or potentially at only one of those two positions (usually the 4-position of the sydnone ring). Further, previous limited studies had shown that selective removal of the iodine on the sydnone ring could be achieved by treatment of the appropriate diiodo-aryl sydnone compound with aqueous sodium sulfite in methanol, a process that was anticipated to be potentially useful in the present work.

Regardless of concerns associated with the apparent potential of *n*-butyllithium to cause metal-halogen exchange to take place on the aryl ring of 3-(4-chlorophenyl) sydnone **107** (X=Cl), it was still chosen as the base of choice for the dilithiation process with **107** (X=Cl) owing to its favorable basicity. Moreover, an authentic product **107** (X=Cl) had been previously characterized in this laboratory and accordingly, it was anticipated that comparisons could be made easily to ascertain the authenticity of the products obtained. The use of LDA as a base in such transformations was known to have posed some problems in the past (presumably because of its reduced basicity compared to *n*-BuLi), and therefore it was reasonable to attempt the use of an alternative base. Indeed, when **116** was reacted with *n*-butyllithium at -78° C in dry THF under an atmosphere of nitrogen gas, followed by exposure to iodine as an electrophile, one of the two products isolated by column chromatography was the expected diiodosydnone **118** (14% yield).

The identity was confirmed by IR and NMR comparisons with previously made authentic sample data. Thus, in the IR spectrum of **118**, strong carbonyl split peaks characteristic of the sydnone ring were present at 1708cm^{-1} and the sydnone C-H stretch at 3112cm^{-1} had disappeared confirming that the sydnone C-4 proton had been replaced. In the ^1H -NMR spectra of **118** the expected substitution pattern of a singlet and two doublets was observed in the aromatic region. The ^{13}C -NMR spectra of **118** revealed, as had been anticipated, three taller peaks indicative of the three sets of aromatic C-H in the aryl ring, five smaller signals indicative of the quaternary carbons present, and a sydnone carbonyl peak at 168ppm. As expected, the C-4 signal was shifted from the usual position for an unsubstituted sydnone ($\sim 94\text{ ppm}$) to 52 ppm, which strongly indicates the substitution of a sydnone proton with an iodo moiety (Scheme 15).

Scheme 15

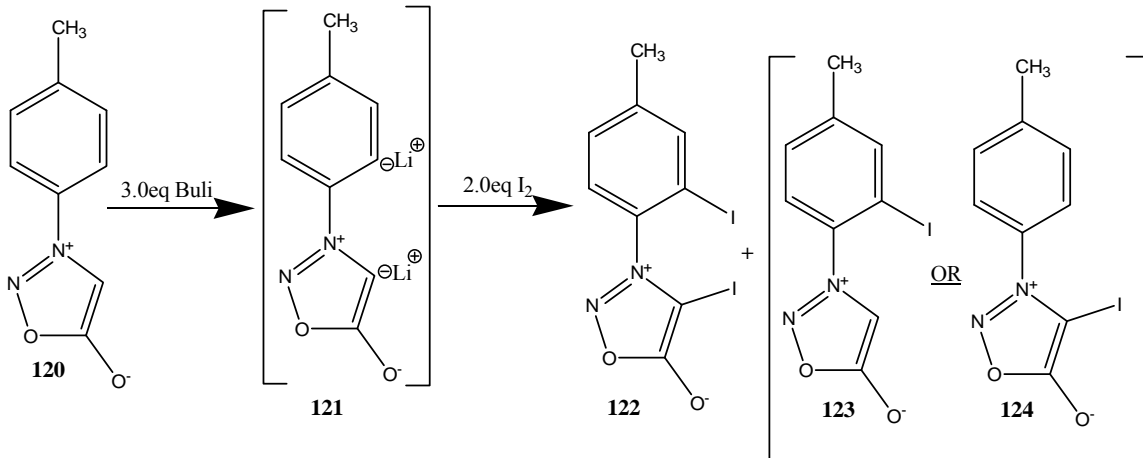


The second product was suspected to be an *ortho*-monosubstituted product **119** as

suggested by its IR spectrum which revealed that the sydnone proton was still present as indicated by the characteristic CH stretch around 3138cm^{-1} . The ^1H NMR spectrum showed a singlet, doublet, doublet pattern in the aromatic (indicative of trisubstitution) and the sydnone C-H proton at chemical shift 6.8 ppm was very visible. The ^{13}C -NMR spectra of **119** revealed, as had been anticipated, three taller peaks indicative of the three different types of aromatic C-H in the aryl ring, five smaller signals indicative of the quaternary carbons present, and a sydnone carbonyl peak at 168.40ppm. The C-4 signal remained in its original position indicating substitution of iodine at the aryl ring rather than the sydnone. The production of this monosubstituted product was anomalous since previous monosubstitutions of arylsydnones by lithiation approaches have taken place only at the sydnone C-4 position rather than the *ortho*-aryl position. This can be rationalized by comparison of the pKa values for the proton at the sydnone C-4 position (pKa~18-20) and that at the C-2 position of the aryl ring (pKa~35-40). The lower pKa value for the sydnone ring proton should mean that its conjugate base would form first in any base abstraction process, allowing reaction with the electrophile, especially if the dianion is not formed. At this stage the only reasonable explanation for the anomalous result is that some of the diidosydnone formed initially might have reacted with sodium sulfite used during the work up process to get rid of excess iodine. We have shown previously that this latter reaction can occur under homogeneous conditions and, while the present washing process should have been effected under strictly heterogeneous conditions, it is possible that unevaporated THF may have allowed sufficient homogeneity to effect the deiodination. The isolation of the target molecule, **118** was especially important in principle since it demonstrated the reproducibility of the

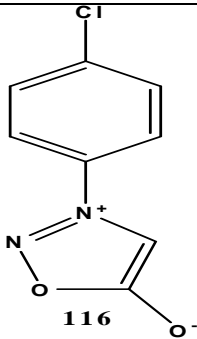
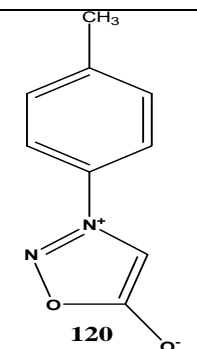
procedure for the lithiation and substitution reaction. It also allayed fears of a potential metal-halogen exchange with the para-*chloro* moiety due to the use of butyllithium as a base. With this potential for successful lithiations in mind, it was decided to attempt another synthesis under the same conditions with the same electrophile but using another aryl sydnone, 3-(4-methylphenyl)sydnone (**120**). It should be noted that this was the first time that an aryl sydnone of this nature had been subjected to lithiation conditions and subsequent treatment with an electrophile and obviously, there were concerns that a proton from the aryl-attached methyl group might be abstracted, complicating the situation. When **120** was treated with 3 equivalents of BuLi at -78°C and subsequently reacted with iodine a very low yield of two products of higher polarity than the starting material resulted. The higher running product (by TLC) was isolated in very low yield by column chromatography (2.8%). The IR spectrum of this product showed a strong carbonyl split peak at $\sim 1714\text{cm}^{-1}$ characteristic of the sydnone ring. Moreover, the sydnone C-H stretch present in the corresponding starting materials had disappeared. In the ^1H -NMR spectrum the expected substitution pattern of two doublets and a singlet in the aromatic region was observed. Unfortunately, the quantities produced at this stage were insufficient for a ^{13}C -NMR spectrum to be run. However, the identity of the isolated product was later confirmed, or at least strongly suggested, as the diiodo sydnone **122** by elemental analysis. The other product was speculated to be either the ortho-iodophenyl sydnone **123** or para-tolyl iodosydnone **124**; however, since no sufficient amounts could be isolated the correct structure of the product could not be elucidated.

Scheme 16



With the apparent positive results for both these preliminary tests the groundwork was laid down for further explorations. Since the identities of the diido sydnone were now known, it became possible to use the samples for TLC analysis of the mixtures obtained on further attempted dilithiations of the two aryl sydnone. At this point it was intended to explore conditions under which the relative yields could be improved and investigate the percentage proportions of the different potential products using different experimental setups. It was thought that the failure to undergo complete substitution with the iodine electrophiles for the sydnone **116** and **120** could be related to the quantities of the reactants, *viz* either insufficient base used owing to the gradual degradation of BuLi over a period of time or insufficient quantities of the electrophile. It was also postulated that the reactions might be slower than expected, necessitating monitoring on several occasions until the desired diido compound was obtained. A study of the dilithiation, and trapping with iodine, of **116** and **120** was thus undertaken, where the amounts of the lithium base as well as iodine used were varied, and the results are summarized in Table

Table 1. Dilithiation of arylsydnones 116 and 120 followed by reaction with iodine

Entry	Starting material	Equivalent material used		Temperature °C	Time	Product Yields%	% weight composition
1*	 116	3eq. BuLi	2.2eq. I ₂	~-60 to -45	Overnight	12:14	61:11:18:10
2**		3.2eq. BuLi	2.2eq. I ₂	~-78	3hrs	49:1	31:67:2:0
3**		3.4eq. BuLi	2.5eq. I ₂	~-78	3hrs	73:1	12:86:2:0
4*		3.5eq. BuLi	2.5eq. I ₂	~-60 to -45	Overnight	0:54	0:0:80:20
5*		3.8eq. BuLi	2.5eq. I ₂	~-60 to -45	Overnight	0:53	0:0:94:6
1*	 120	3eq. BuLi	2.2eq. I ₂	~-60 to -45	4hrs	0:3	96:0:4:0
2*		3eq. BuLi	2.3eq. I ₂	~-60 to -45	Overnight	1:26	52:1:47:0
3**		3eq. BuLi	2.3eq. I ₂	~-78	Overnight	7:0	58:42:0:0
4**		3.2eq. BuLi	2.2eq. I ₂	~-78	2hrs 30min	68:2	24:73:3:0
5**		3.2eq. BuLi	2.2eq. I ₂	~-78	2hrs 30min	73:1	9:89:2:0
6*		3.4eq. BuLi	2.2eq. I ₂	~-60 to -45	Overnight	3:75	29:1:70:0

Key

% yields; monoiodo compound: diiodo compound.

% compositions; starting material: monoiodo compound: diiodo compound: impurities

*predominantly dry ice, dry/ ice acetone bath used to cool the reaction.

**predominantly acetone, dry ice/acetone bath used to cool the reaction.

The reactions of 3-(4-chlorophenyl)sydnone (**116**) and 3-(4-tolyl)sydnone (**120**) with n-butyllithium then iodine (Table 1) were set up in 3-necked flasks or Erlenmeyer flasks as necessary and a magnetic stirrer was inserted into the reaction vessel prior to flame drying under an atmosphere of dry nitrogen. After cooling to the appropriate temperature and addition of the reactants, TLC monitoring was achieved at different reaction times by insertion of a flame-dried syringe into the reaction vessel through a septum and then withdrawal of some of the reaction contents.

As previously reported, it was anticipated that increasing the amounts n-BuLi from 3.0 equivalents would favor the formation of the desired diiodo product, however, the results as shown in Table 1, appear to suggest a different trend. It was discovered during the investigations that slight temperature variations appeared to favor certain products over others. It was thought that this could potentially allow selective production of mono or diiodo sydnones, which could then be fully characterized and identified. Thus, since temperatures associated with the cooling bath were determined by the composition of the cooling bath it was thought that different results could be obtained through use of different experimental setups with either a cooling bath where the *dry ice predominates* over acetone or one in which *acetone predominates* over dry ice. The premise for this conjecture was based on the expectation that some products produced in the reactions are thermodynamic products whereas others are kinetic products. With this line of thinking it was postulated also that those reactions which would produce thermodynamic products would potentially require lengthy periods of reaction times whereas those that produce kinetic products would require shorter durations. A cooling bath in which acetone predominates would be more efficient in lowering the temperatures as the solvent

facilitates the passage of heat from the reaction through convection currents and would thus be suitable for the kinetic reaction. In contrast, a cooling bath in which dry ice predominates would be less efficient and thus produce a range of increasing temperatures, which would be useful for the thermodynamic reaction. To avoid unnecessary wastage of the dry ice through evaporation, the cooling baths were covered with aluminum foil and, this, in addition to the use of a Dewar bath, helped in maintaining a relatively constant temperature, as required.

As can be seen in Table 1, the diiodo compounds **118** and **122** were favored when temperatures were allowed to rise, as in a *predominantly dry ice*, dry ice acetone bath, kept for longer durations. This appears to confirm an earlier assertion that in the absence of TMEDA excess amounts of BuLi could be used at higher temperatures to achieve dilithiation of arylsydnones. However, in some cases, there appear to be consequences associated with this assertion, particularly as reflected by the generation of impurities. For instance, in the case of the lithiation / iodination reactions of **116**, a high running (on TLC), unidentified, less polar product was obtained when large quantities of BuLi were used and temperatures were allowed to rise. The main product was isolated by column chromatography and its IR spectrum showed an OH stretch at 3375cm^{-1} and an aliphatic CH stretch around 2959cm^{-1} . This was suspected to be as a result of the slow reaction between BuLi and the THF solvent generating electrophiles, which subsequently reacted with the sydnone **116**.

More interesting results were obtained when temperatures were lowered and kept almost constant in the *predominantly acetone*, dry ice/acetone bath. A product slightly lower running than the diiodo compounds **118** and **122** was obtained as a predominant product

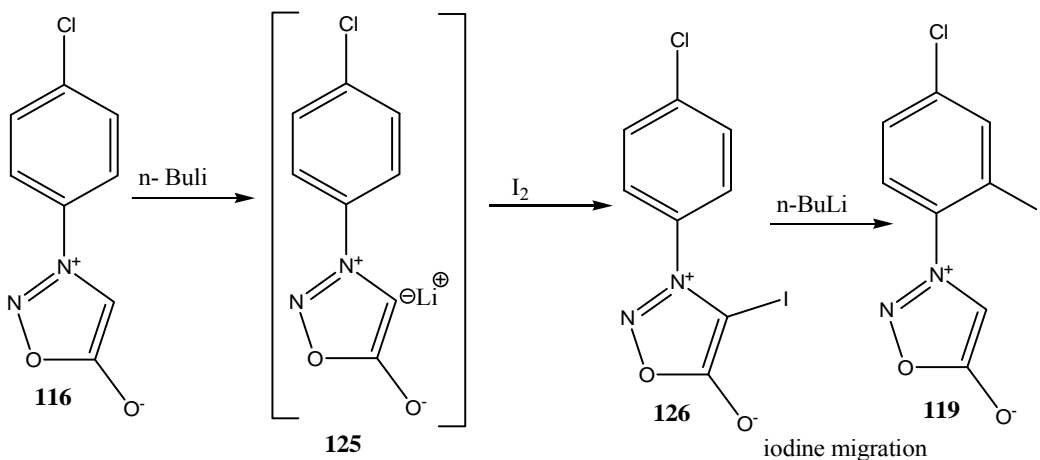
together with traces of the diiodo compounds **118** and **122** as well as starting material. When the main products were compared by TLC with authentic materials produced through reduction of **118** and **122** using sodium sulfite, which will be discussed later, they were found to be of the same polarity and were thus suspected to be the *ortho*-monosubstituted sydnones **119** and **123**. Confirmation of their identities as **119** and **123** was made through their full characterization by IR, NMR and elemental combustion analysis. Thus, the I.R spectra of **119** and **123** each included a sydnone carbonyl stretch at 1727cm^{-1} and a characteristic sydnone C-H stretch at 3139 and 3137cm^{-1} , respectively. The ^1H -NMR spectra of **119** and **123** both showed the sydnone C-4 proton at about 6.58ppm . The ^{13}C -NMR spectrum of **119**, as expected for the *ortho*-iodo species, had a total of eight peaks including the sydnone C-5 (168.40ppm), the C-4 (97.63ppm), the carbon of the aromatic ring attached to iodine (92.55ppm) and the five remaining aromatic carbons, which were present between 127.40 and 140.46ppm . The ^{13}C -NMR spectrum of **123** had a total of nine peaks including the sydnone C-5 (168.68ppm), the C-4 (97.71ppm), the carbon of the aromatic ring attached to iodine (91.60ppm) and the five remaining aromatic carbons, which were present between 126.31 and 144.64ppm . As stated earlier, the production of **119** and **123** was anomalous. The pK_a values for the sydnone proton (pK_a 18-20) and the *ortho*-aryl proton (pK_a 35-40) would predict that the anion at the sydnone 4-position would be formed first. Previous findings from our laboratory have shown that when these lithiation reactions do not occur cleanly, mono *ortho*-substituted arylsydnones are not formed unless the electrophile is weak. This latter situation is not the case with iodine and no other arylsydnone has provided selective reaction at only the *ortho*-aryl position with this electrophile. Accordingly, due to the

unprecedented nature of the present finding, it was assumed initially that the products **119** and **123** could have been produced by deiodination of the diiodo compounds **118** and **122** during the work up process with sodium sulfite. The latter has been shown previously in our laboratory to effect clean removal of an iodo (or bromo) functionality from the sydnone 4-position. However, this conjecture was shelved after a TLC examination prior to addition of the sodium sulfite showed the presence of the *ortho*-iodo compounds **119** and **123** as predominant products. While the controversial production of **119** and **123** using BuLi merits further investigation, it is worthwhile noting that some previous investigations in our laboratory have revealed that LDA, an organolithium, but less basic, base like BuLi, is an effective way to shift a tert-butyldimethylsilyl species substituted at the sydnone 4-position to the *ortho* aryl position.¹⁸ Although other bases such as n-BuLi, sec-BuLi and t-BuLi failed to achieve the same result, it was thought at that time that this was due to the bulkiness of the silyl group which was attached to the sydnone C-4 position. Accordingly, with this previous observation in mind, one mechanism that can be postulated for the present rather unusual reaction leading to the *ortho*-iodophenyl-sydnones **119** and **123** involves the formation of the *para*-iodophenylsydnones **124** and **126** at extremely low temperatures followed by a rearrangement of the iodine moiety (Scheme 17). Although, no tangible evidence for the intermediacy of the *para*-iodophenyl-sydnones **124** and **126** was apparent by TLC, slight changes in the reaction setup involving the use of a Dewar bath with a larger circumference, thus subjecting the reaction to slight temperature variations, revealed a very dilute spot slightly higher running than starting material but lower running compared to the *ortho*-

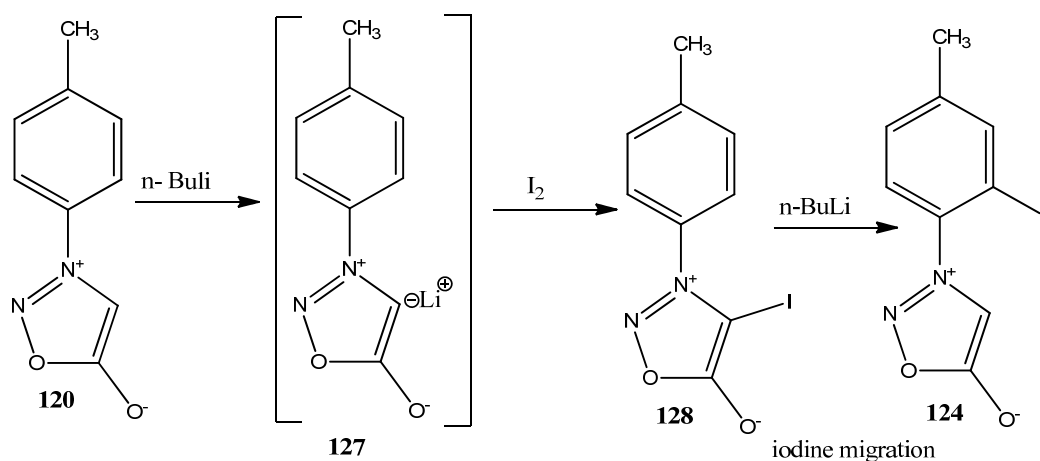
iodophenylsydnone **119**, which unfortunately could not be isolated presumably since it was in negligible amounts.

Scheme 17

a)



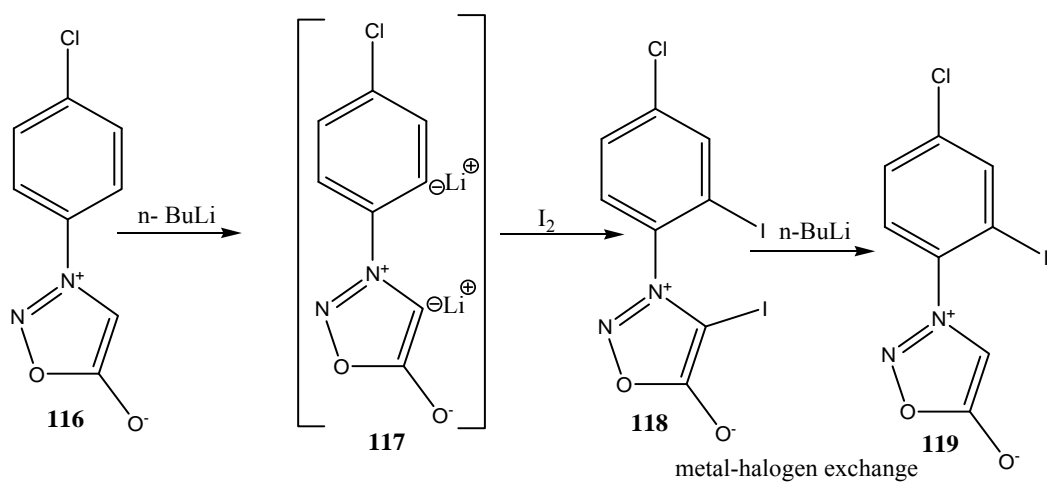
b)



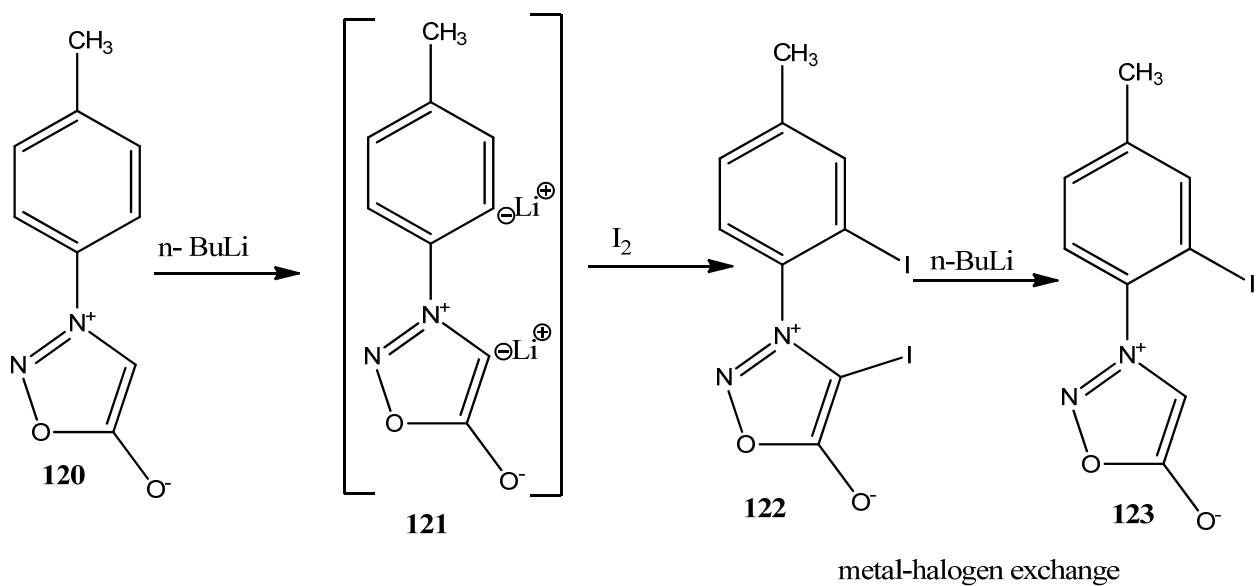
Another possible mechanism for the formation of **119** and **123** is the formation of the diiodo compounds **118** and **122** followed by the subsequent removal of the sydnone-attached iodine by a selective metal-halogen exchange reaction (Scheme 18).

Scheme 18

a)



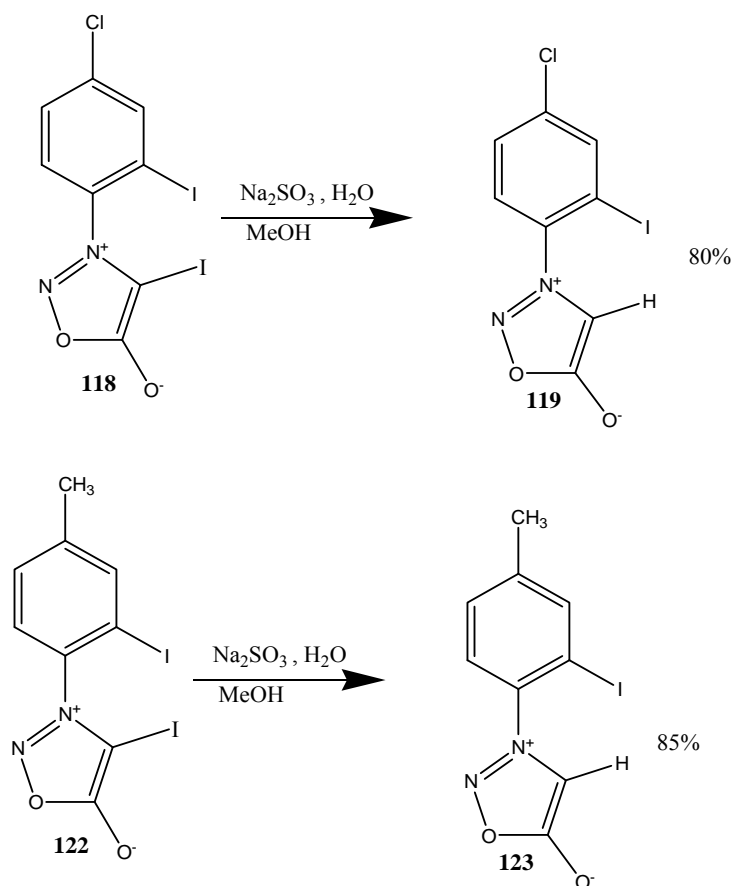
b)



2. Attempted selective reduction reactions of 3-(4-chloro-2-iodophenyl)-4-iodosydnone (118) and 3-(4-methyl-2-iodophenyl)-4-iodosydnone (122).

With these unusual but gratifying results (discussed on pages 56-59), it was elected to try possible alternative avenues for the synthesis of the *ortho*-iodophenylsydnones **119** and **123**. As mentioned earlier, it is possible to remove iodine attached at the sydnone 4-position using sodium sulfite. Accordingly, it seemed likely that compounds **119** and **123** could be prepared by an alternative approach (partly for structural confirmation) from their diiodo congeners **118** and **122**, respectively by sodium sulfite reduction, especially since the diiodo compounds had been synthesized in satisfactory yields. As expected, the reduction of 3-(4-chloro-2-iodophenyl)-4-iodosydnone (**118**) with sodium sulfite solution in methanol yielded the desired *ortho*-iodophenylsydnone **119** in high yield (80%) as shown in Scheme 19 below. Similarly, the reduction of 3-(4-methyl-2-iodophenyl)-4-iodosydnone (**122**) with sodium sulfite solution in methanol yielded the desired *ortho*-iodophenylsydnone **123** in high yield (85%) as shown in the same scheme.

Scheme 19



When the products **119** and **123** were compared by TLC to the products previously synthesized *via* lithiation reactions they were seen to be identical. Additionally, **119** had been synthesized previously in this lab and fully characterized, which allowed further comparisons to be made and the material prepared by the present method was shown to be identical. In addition, the IR, ^1H -NMR and ^{13}C -NMR spectra of **123** were shown to be the same as those of the *ortho*-iodo species **123** prepared by the lithiation protocol discussed previously. It can be concluded that the yields in this case are similar to those

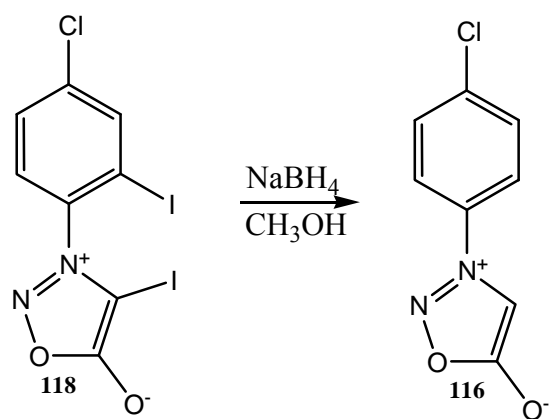
obtained previously in our laboratory, however, the overall yield, taking into account the synthesis of their precursors, the diiodo compounds **118** and **122** (54% and 75%, respectively), is much better compared to the modest yields previously reported. As stated earlier this is undoubtedly attributable to the higher basicity of BuLi compared to LDA.

However, a comparison of the two step reactions with the recently discovered one step synthesis of *ortho*-iodophenylsydnones **119** and **123**, directly from **116** and **120**, (as reported on pages 56 to 59) shows that the one step process (Schemes 17 and 18) is more efficient. However, extension of this one step approach to other substituted arylsydnones may not always be effective, e.g. for *meta*-substituted arylsydnones there may be issues with the lowering of electron density, such as in the case of a substituted *meta*-halogen on the aryl ring, or steric hindrance.

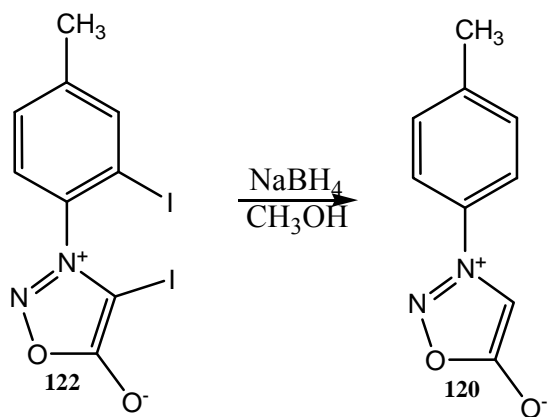
Since we had shown previously that bromine and iodine atoms attached to the sydnone ring could be removed under mild conditions using sodium sulfite and sodium borohydride, separately, the main focus was now on investigating the scope of the process by which the disubstituted species **118** and **122** could be reduced using sodium borohydride as a reducing agent. From a brief, previous study in our laboratory it had been shown that, surprisingly, treatment of 3-(2-iodophenyl)-4-iodosydnone (**102**, X=H) with sodium borohydride resulted in removal of both iodines to yield 3-phenylsydnone (**5**, R'=Ph, R=H). The parameters for this process had not been ascertained and, accordingly, the starting point was to test the reactions of **118** and **122** with sodium borohydride to check whether selective reduction would or would not take place, with the expectation that the fully reduced products would be obtained (Scheme 20).

Scheme 20

a.



b.

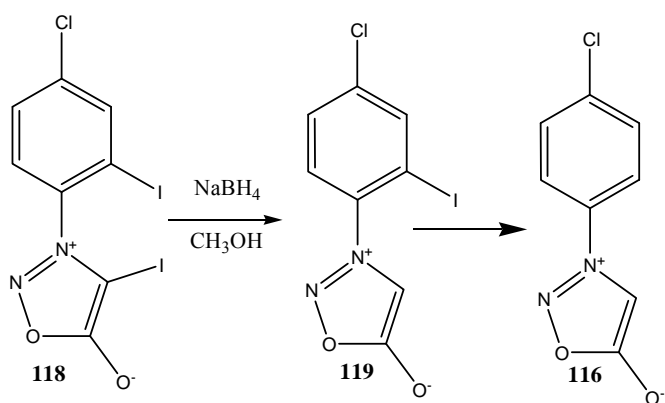


Indeed, as had been anticipated, when 3-(4-chloro-2-iodophenyl)-4-iodosydnone (**118**) and 3-(4-methyl-2-iodophenyl)-4-iodosydnone (**122**) were treated separately with NaBH_4 in methanol with stirring at room temperature, different compounds from the starting material were observed in each case (lower running on TLC compared to the starting material). After isolation, the IR spectrum for the product from the reaction involving 3-

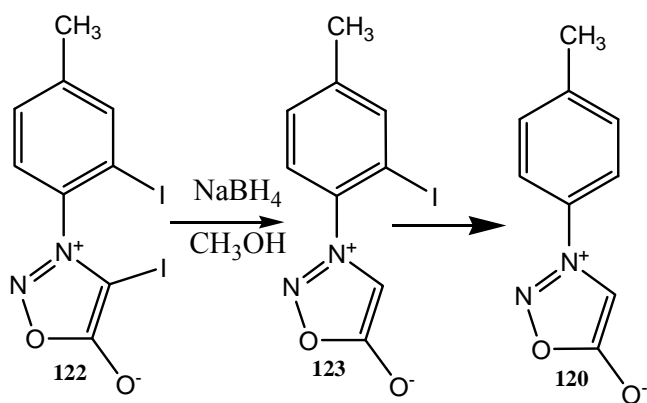
(4-methyl-2-iodophenyl)-4-iodosydnone (**122**) showed the product to be the completely deiodinated compound 3-(4-methylphenyl)sydnone (**120**), which was obtained in 87% yield. Surprisingly, the reduction of 3-(4-chloro-2-iodophenyl)-4-iodosydnone (**118**) with sodium borohydride gave a product which was different from both the starting material **118** and the fully deiodinated material **116**. It was suspected that this unusual product could be the *ortho* iodo species **119**. Using this premise, the infrared spectrum of the product displayed the expected peak for the sydnone C-H stretch at about 3137cm^{-1} , indicative of the removal of the iodine at the C-4 position, and a strong peak at 1725cm^{-1} for the C=O stretch of the sydnone ring. The ^1H NMR spectrum displayed a singlet at around 6.8ppm, clear indication that the iodine at the C-4 position had been removed. In the aromatic region two doublets at 7.65 and 7.85ppm, consistent with the long range coupling of two protons with another *meta* proton, were observed, together with a singlet at 8.00ppm for the *meta* proton. The ^{13}C NMR spectrum showed three taller peaks indicative of the three different types of aromatic C-H in the aryl ring, five smaller signals indicative of the quaternary carbons present, and a sydnone carbonyl peak at 168.39ppm. As this was a rather unusual observation, from previous findings in our laboratory, it was decided to carefully repeat the reactions for both 3-(4-chloro-2-iodophenyl)-4-iodosydnone (**118**) and 3-(4-methyl-2-iodophenyl)-4-iodosydnone (**122**) and monitor each by TLC to see the exact quantities of NaBH_4 required to remove one or both iodine moieties. As such, it was elected to investigate the feasibility of the process shown in Scheme 21 below.

Scheme 21

a.

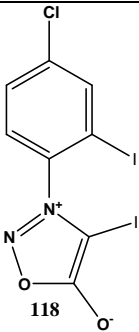
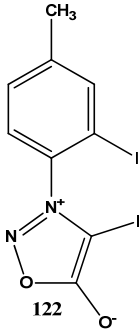


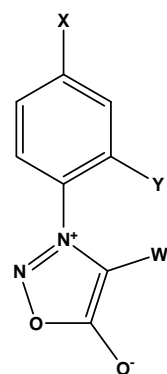
b.



The results obtained from these investigations are summarized in Table 2 below:

Table 2: Reduction reactions of 3-(4-chloro-2-iodophenyl)-4-iodosydnone (118**) and 3-(4-methyl-2-iodophenyl)-4-iodosydnone (**122**) with NaBH₄.**

Starting material	Entry 1		Entry 2		Entry 3	
	NaBH ₄	Products	NaBH ₄	Products	NaBH ₄	Products
 <p>118</p>	12 equiv.	116 (23%)	3 equiv.	116 ;119	1.2 equiv	116;118;119
			6 equiv.	116 ;119	2.4equiv	116;119
			9equiv.	116 (32%)	3.6equiv	116 ;119
					7equiv	116 (46%)
 <p>122</p>	34equiv	120 (87%)	3 equiv.	120;123	0.6equiv.	122,123
			6 equiv.	120;123	1.2equiv	122,123
			12 equiv.	120;123	2.1equiv	123 (97%)
			15 equiv.	120;123		
			18equiv	120;123		
			24equiv	120;123		
			35equiv	120 (36%)		



119. X = Cl,
Y = I, W = H

116. X = Cl,
Y = W = H

123. X = CH₃,
Y = I, W = H

120. X = CH₃,
Y = W = H

As can be seen in Table 2, upon treatment with 3 equivalents of NaBH₄, and tracking by TLC, two products (entry 2) were seen for both reduction reactions of 3-(4-chloro-2-iodophenyl)-4-iodosydnone (**118**) and 3-(4-methyl-2-iodophenyl)-4-iodosydnone (**122**). By comparison with authentic samples it was shown that these products were the *ortho*-iodo species, **119** and **123**, and the fully deiodinated compounds, **116** and **120**.

Accordingly, it was elected to move from here in two directions, viz., one, to add more NaBH₄ in an attempt effect complete reduction (entry 2) and, two, to add less NaBH₄

initially in an attempt to explore the possibility of selective removal of only the 4-iodo moiety (entry 3). Accordingly, treatment of **118** and **122** with 6 equivalents of NaBH₄ was explored. In both cases, as shown in Entry 2, a mixture of the corresponding *ortho*-iodo and deiodo species resulted and it was elected to investigate the ramifications of increasing the amount of NaBH₄ yet further. As expected, with the chloro species **118** and 9 equivalents of NaBH₄, complete deiodination occurred to yield **116** in 32% yield (confirmed by comparison with an authentic sample). Surprisingly when **122** was treated with 12, 15, 18 or 24 equivalents of NaBH₄ a mixture of the *ortho* iodo and deiodo congeners **120** and **123** resulted and it was not until the addition of 34 equivalents (entry 1) or 35 equivalents of NaBH₄ that complete conversion to the deiodinated material **120** resulted. No reasonable explanation for this dichotomy is apparent. To explore whether or not selective iodine removal was possible (entry 3), compound **118** was treated first with 1.2 equivalents of NaBH₄. This process resulted in a mixture of 3 products (starting material, *ortho*-iodo **119** and deiodo **116** sydnones). Accordingly, the amount of NaBH₄ was increased to 2.4 equivalents, 3.6 equivalents and, finally, 7 equivalents. Strangely, despite the initial success in preparing the *ortho*-iodo species **119** from **118** by this approach (with 12 equivalents of NaBH₄, page 64), these transformations led to mixtures or the fully reduced compound **116** (in 46 % yield).

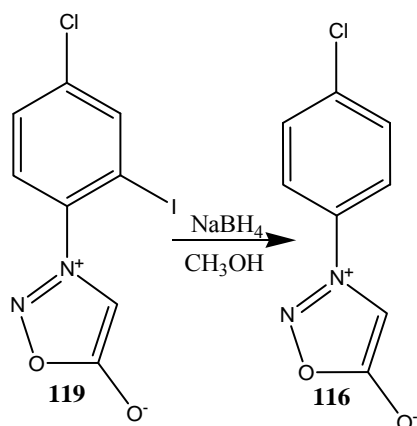
Armed with this knowledge, the first attempt at selective reduction of **122** was conducted with 0.6 equivalents of NaBH₄ (entry 3) and, perhaps not surprisingly, this led to a mixture of **122** and **123**. A similar result was obtained with 1.2 equivalents but, surprisingly, when the reaction was repeated with 2.1 equivalents, a high yield (97%) selective conversion to the *ortho*-iodo species **123** was observed. The product was

identified by comparison (TLC, IR, and mp) with an authentic sample. The conclusions that can be drawn from this work (Table 2) are that complete reduction of the iodine moieties is possible with both starting materials and partial reduction (removal of the 4-iodo group) can be achieved for the diiodotolylsydnone **122**. Explanations for some of the results will have to await further studies.

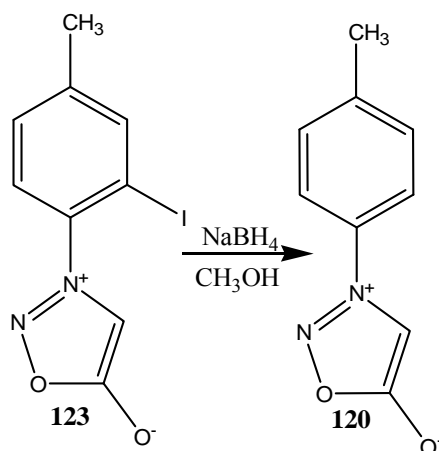
It was then elected to make a follow up on the proposed reaction pathway by subjecting the intermediates **119** and **123** to sodium borohydride reduction. As such, the reactions highlighted in scheme 22 were investigated with the expectation that the fully reduced products would be formed.

Scheme 22

a.



b.

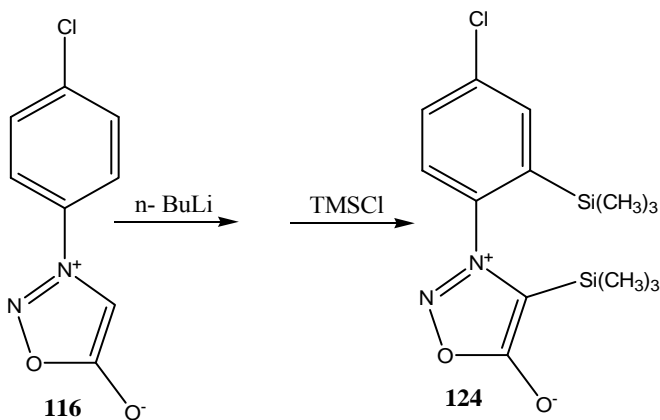


Indeed, when **119** and **123** were treated with 8.7 equivalents and 4 equivalents of sodium borohydride in methanol, respectively, a polar product slightly lower running compared to starting material was obtained in each case. The identities of the products (as **116**; 34.5% yield and **120**; 77% yield) were confirmed later by comparison with authentic samples (TLC, IR). Thus the premise that the intermediacy of the *ortho*-iodo species **119** and **123** precedes the formation of the completely deiodinated species **116** and **120** is supported by these findings.

3. Silylation of arylsydnones **116** and **120** using lithiation techniques.

Since lithiation techniques had proven to be useful in the synthesis of both the disubstituted iodo phenylsydnones **118** and **122** as well as the monosubstituted *ortho* iodophenylsydnones **119** and **123**, it was of interest to repeat the same methodologies using organic electrophiles and test whether the same trend observed with iodine electrophiles applies generally. The organic electrophile chosen for these reactions was chlorotrimethylsilane (TMSCl), since it has a reactivity profile similar to that of iodine. Initial attempts on the lithiation of **116** using 3 equivalents of BuLi followed by treatment with 2 equivalents of chlorotrimethylsilane yielded starting material and impurities. It was then inferred that the amount of BuLi used in this case was not sufficient to abstract both protons from the *ortho*-aryl and sydnone-4 positions of **116** and, thus, the dianion intermediate necessary for the reaction to proceed was not achieved. Using this premise, 3-(4-chlorophenyl) sydnone (**116**) was then reacted with 4 equivalents of BuLi at -78°C under dry nitrogen conditions followed by 2.9 equivalents of chlorotrimethylsilane. The outline of the reaction and the expected product is shown in Scheme 23.

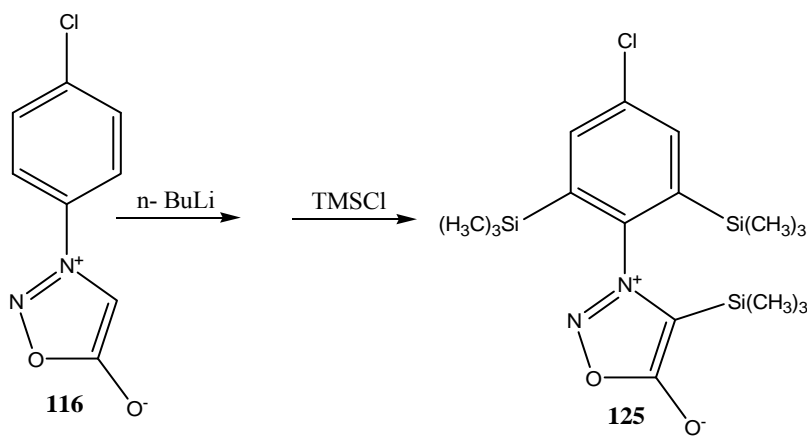
Scheme 23



Unfortunately, this modified attempt at transforming 3-(4-chlorophenyl) sydnone **116** to 3-(4-chloro-2-(trimethylsilyl) phenyl)-4-trimethylsilylsydnone **124** using the dilithiation protocol followed by treatment with TMSCl yielded five products of lower polarity in comparison to starting material (TLC). After separation and purification by column chromatography followed by multiple recrystallizations, one sydnone derivative was isolated as proven by IR and NMR. The four other products were inferred to be non-sydnone impurities as revealed by their IR spectra which clearly showed an amine band at around 3379cm^{-1} in each case. It is likely that the sydnone ring could have broken down during the course of the reaction. The IR of the isolated sydnone derivative showed a strong peak at 1737cm^{-1} , indicative of the C=O stretch for the sydnone ring, and no evidence of the CH stretch at $\sim 3100\text{cm}^{-1}$, indicative of substitution of the sydnone C-4 position. The spectrum also showed some medium peaks around 2960cm^{-1} , indicative of aliphatic substitutions. However, in the proton NMR spectrum, two strong, separate singlet peaks were revealed at around 0 ppm, together with a smaller singlet peak at 7.45 ppm. The peaks had an integration ratio of approximately 5:10:1. This led to the speculation that the product produced in this case was in fact trisubstituted rather than disubstituted, and the trimethylsilyl groups attached to the *ortho* aryl positions were different from those attached to the sydnone C-4 position. In the ^{13}C NMR spectrum, again two peaks were revealed at about 0 ppm, and their relative intensities were almost 1:2. In addition, six quaternary peaks were also evident, including the peak at 173.64 ppm indicative of the sydnone C=O, and another peak at 109.89 ppm, indicative of substitution at the sydnone C-4 position. The other four, short peaks were within the aromatic region, indicative of four substituted carbons on the aryl ring and one taller peak, indicative of

the two equivalent non-quaternary aryl protons. These spectra together with the elemental analysis results suggest the formation of the trisubstituted product, 3-(4-chloro-2, 6-di(trimethylsilyl) phenyl)-4-trimethylsilylsydnone (**125**), in 30 % yield rather than the disubstituted product, 3-(4-chloro-2-(trimethylsilyl) phenyl)-4-trimethylsilylsydnone (**124**), as illustrated in Scheme 24,

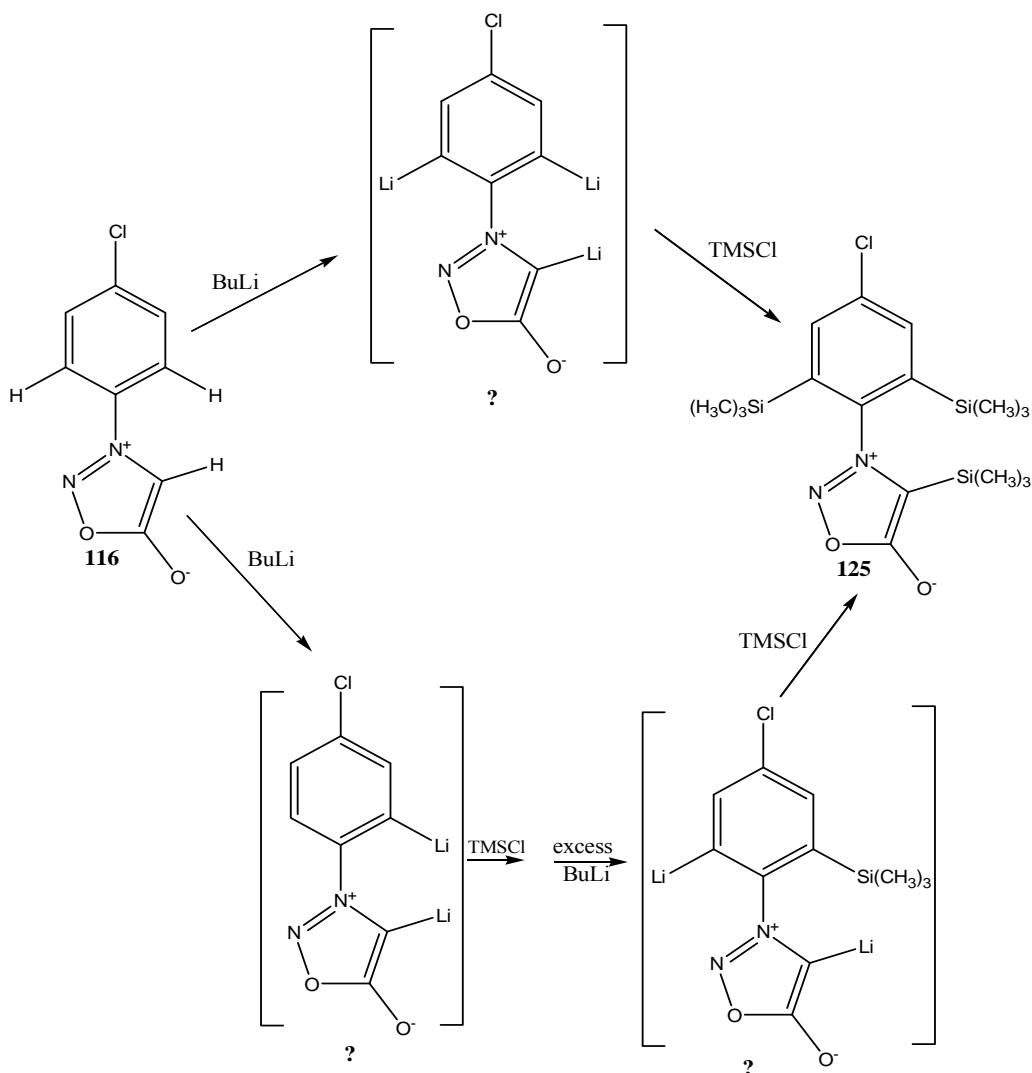
Scheme 24



As noted earlier, previous research in our laboratory revealed that the sydnone ring can act as an *ortho* director of lithiation and, when arylsydnones are treated with at least 2 equivalents of a strong lithium base, dilithiated sydnones such as **117** and **121** are produced. However, using this line of reasoning, the formation of a trisubstituted species **125**, suggests the formation of a trianion intermediate. This seems very unlikely since the formation of such a trianion would be very energetically unfavorable. Accordingly, it was elected to perform further investigations with the intent to rationalize this unusual transformation. In that regard, it should be noted, that this is not the first time that such a transformation has been reported in our lab, and, recently, Turnbull and Dossa reported the likely formation of triiodo arylsydnones upon treatment of arylsydnones with excess

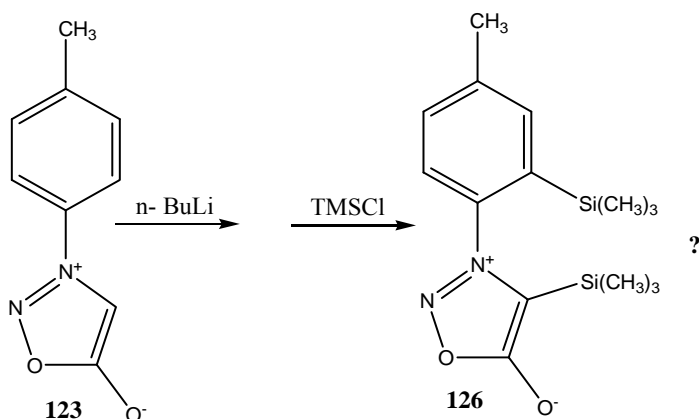
LDA followed by exposure to an iodine electrophile.¹⁰⁷ Drawing upon the rationale reported earlier by Turnbull and Dossa, it seems likely that for the present case, two possible pathways exist for the generation of the trisubstituted species **125**. The first pathway, as suggested for the iodination situation, would involve the formation of a trianion initially, followed by subsequent trisubstitution. An alternative pathway would involve the formation of a dianion initially, which then could react selectively at the *ortho* position of the ring upon exposure to an electrophile. The resulting sydnone anion would still be subject to sydnone ring directed abstraction of the remaining *ortho* proton, which, upon further reaction with chlorotrimethylsilane, would lead to **125** (Scheme 25)

Scheme 25



As a continuation of this work, it was elected to attempt a dilithiation reaction with **120**, followed by subsequent exposure to chlorotrimethylsilane, with the intent of exploring whether or not a disubstituted product, 3-(4-methyl-2-(trimethylsilyl) phenyl)-4-trimethylsilylsydnone (**126**) or a trisubstituted congener would result (Scheme 26).

Scheme 26



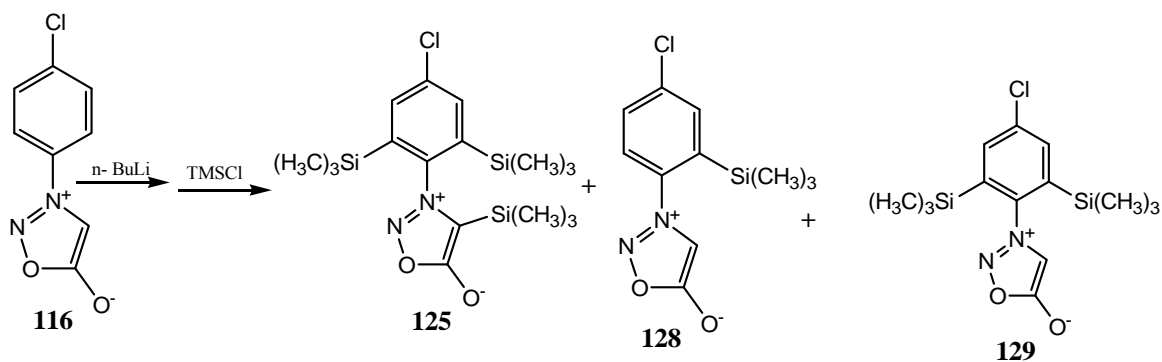
When **123** was treated with 4 equivalents of BuLi, followed by exposure to 2.9 equivalents of chlorotrimethylsilane, a brown oil was recovered after work up and two products of lower polarity compared to the starting material were observed by TLC, together with some starting material. Upon separation of the two products by column chromatography and subsequent recrystallizations the higher running product, brown oil, was examined by IR spectroscopy and inferred to be a non-sydnone compound. Thus, IR of this non-sydnone impurity showed an NH stretch doublet characteristic of primary amines at around 3376.90cm^{-1} , and strong aliphatic bands at 2957.56cm^{-1} and 2872.31cm^{-1} , respectively. The IR spectrum also revealed a strong sharp peak at 1731.15cm^{-1} , characteristic of an ester and a very complex fingerprint region. It was inferred that the impurity might have been generated as a result of a breakdown in the sydnone ring. The other product however, was shown to be a sydnone derivative viz. 3-(4-methyl-2-(trimethylsilyl) phenyl)-4-trimethylsilylsydnone (**126**) by its spectral data. Thus, as expected, the IR spectrum of **126** revealed a strong sydnone C=O peak at 1737cm^{-1} , moderate aliphatic bands, ranging from 3046 to 2900cm^{-1} , and the absence of the sydnone CH stretch at about 3145cm^{-1} . In the $^1\text{H-NMR}$ spectrum, a singlet was

observed at around 7.35ppm, as well as two doublets at around 7.15 and 7.30ppm, respectively. The presence of the two strong peaks indicative of the two trimethylsilyl groups at around 0ppm was also obvious as was the absence of the sydnone CH peak at around 6.8ppm. In the ^{13}C spectrum also supported the characterization of the product as **126**, showing five quaternary peaks, as well as six non-quaternary peaks. In the aromatic region, three quaternary peaks, indicative of three substituted carbons, as well as three non-quaternary peaks, indicative of unsubstituted carbons, were observed. The presence of the sydnone C=O peak at ~174ppm was also noticeable as was the sydnone C-4 at ~106ppm. There was no sign of a trisubstituted product in the reactions with **123**. It is unclear why.

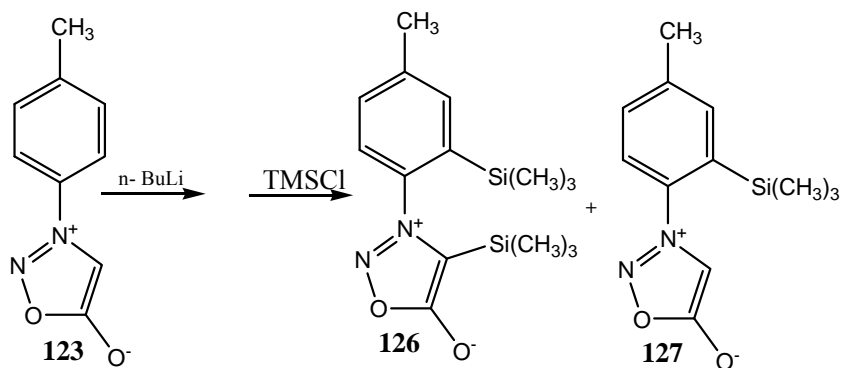
In an attempt to expand the utility of these processes, it was thought that the use of different quantities of BuLi and chlorotrimethylsilane as well as changing physical parameters, particularly temperature, might also generate the ortho substituted species **127** and **128** as was observed when iodine was used as an electrophile. Thus, an investigation was carried out by treating **116** and **123** with different quantities of BuLi, ranging from 3.7 to 6 equivalents, and varying amounts of chlorotrimethylsilane. The reactions of **116** with different quantities of BuLi essentially gave rise to three sydnone products, whereas **123** reacted to give two sydnone products, as outlined in Scheme 27 and Table 3.

Scheme 27

a)

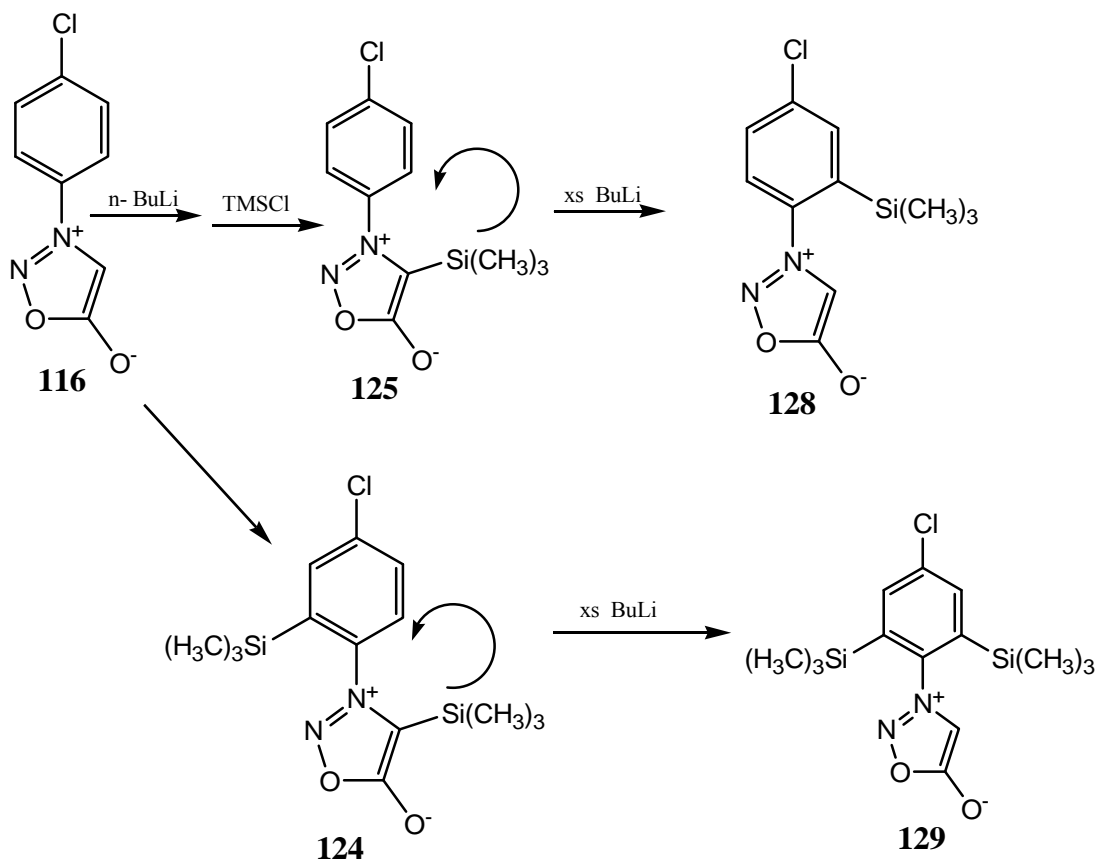


b)



It was thought that the elementary processes that led to products **127**, **128** and **129** might have involved silyl migrations as illustrated in Scheme 28.

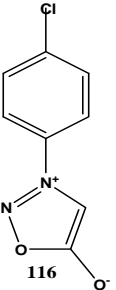
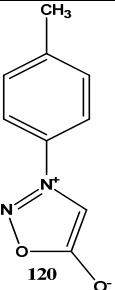
Scheme 28



The driving force for this migration may well be the stability of the anion created at the sydnone-4 position if intramolecular silyl group migration occurs.

The tabulated results for the reactions of **116** and **123** are summarized in Table 3,

Table 3: Lithiation of arylsydnones 116 and 120 followed by reaction with chlorotrimethylsilane

Entry	Starting material	Equivalent material used		Temperature °C	Time	Product Yields%	% weight composition
1	 116	3.7eq.BuLi	2.7eq.TMSCl	~-78	2hrs	20:20:10	20:20:28:32
2		4 eq.BuLi	3 eq TMSCl	~-60 to -45	Overnight	20:0:30	14:20:53:13
3		4.5eq.BuLi	3eq TMSCl	~-60 to -45	2hrs 30min	23:37:0	9:22:46:23
4		5 eq.BuLi	4 eq TMSCl	~-78	3 hrs	5:36:14	0:5:54:26:15
5		6 eq.BuLi	4 eq. TMSCl	~-78	2hrs 30min	0:20:0	0:0:20:80
1	 120	3.8 eq.BuLi	2.2eq.TMSCl	~-78	2hrs 30min	20:0	33:26:0:41
2		3.8eq.BuLi	2.5eq.TMSCl	~-60 to -45	Overnight	20:1	22:24:6:48
3		4eq.BuLi	2.9eq.TMSCl	~-60 to -45	Overnight	3:40	18:2:53:27
4		4.4eq.BuLi	4eq. TMSCl	~-78	2hrs 30min	43:7	4:56:9:31
5		5eq.BuLi	3eq. TMSCl	~-78	3hrs	0:0	0:0:0:100

Key

% yields; monosubstituted compound: disubstituted compound, trisubstituted compound.

% compositions; starting material: monosubstituted compound: disubstituted compound /trisubstituted compound: impurities

Note: The disubstituted product produced from **116** was **129**, whereas **123** produced disubstituted product **126**.

Even though no obvious trend is apparent, it can be argued from the results that, in the absence of extraneous factors, the general thermodynamics and kinetics of these reactions favor the formation of trisubstituted and disubstituted products when temperatures are allowed to rise beyond -78°C and the reaction allowed to go for a longer time. The use of

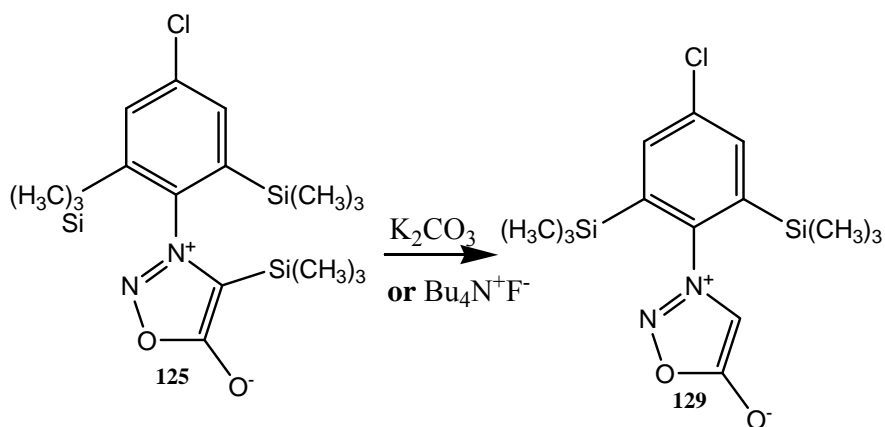
large quantities of BuLi was expected to give rise to the desired dianions and trianions. However, *ortho* monosubstitution was still observed, which led to speculation that silyl group migrations were also contributing to the generation of the products as outlined earlier in scheme 28. However, the increasing trend observed in the percentage composition of non-sydnone impurities as more quantities of BuLi were added strongly supports the formation of unstable trianion species, which are speculated to have contributed to the destabilization and final breakdown of the sydnone ring resulting in significant impurities, which were difficult to purify. The same trend also shows that for almost the same amounts of BuLi and chlorotrimethylsilane more impurities were generated for the tolyl sydnone **120**, compared to the chlorophenyl sydnone **116**. This again appears to support the formation of trianion species, in which case an electron donating methyl group appears to further destabilize the sydnone ring by pushing negative charge through the phenyl ring. In contrast, the electron withdrawing chlorine moiety on **116** would accommodate some of the negative charge thus helping to preserve the sydnone ring.

Attempted selective desilylation of silylsydnones

Previously, it had been shown that silyl groups could be selectively removed from silylsydnones using aqueous potassium carbonate or tetrabutylammonium fluoride. Since, in the present work, a new trisilylsydnone **125** and a new disilylsydnone **126** had been prepared, it was of interest to see whether the silyl group could be selectively removed from the sydnone ring. As a follow up to these investigations it was also elected to use the newly formed *ortho* silylated sydnones (viz **127**, **128** and **129**) in similar reactions. As

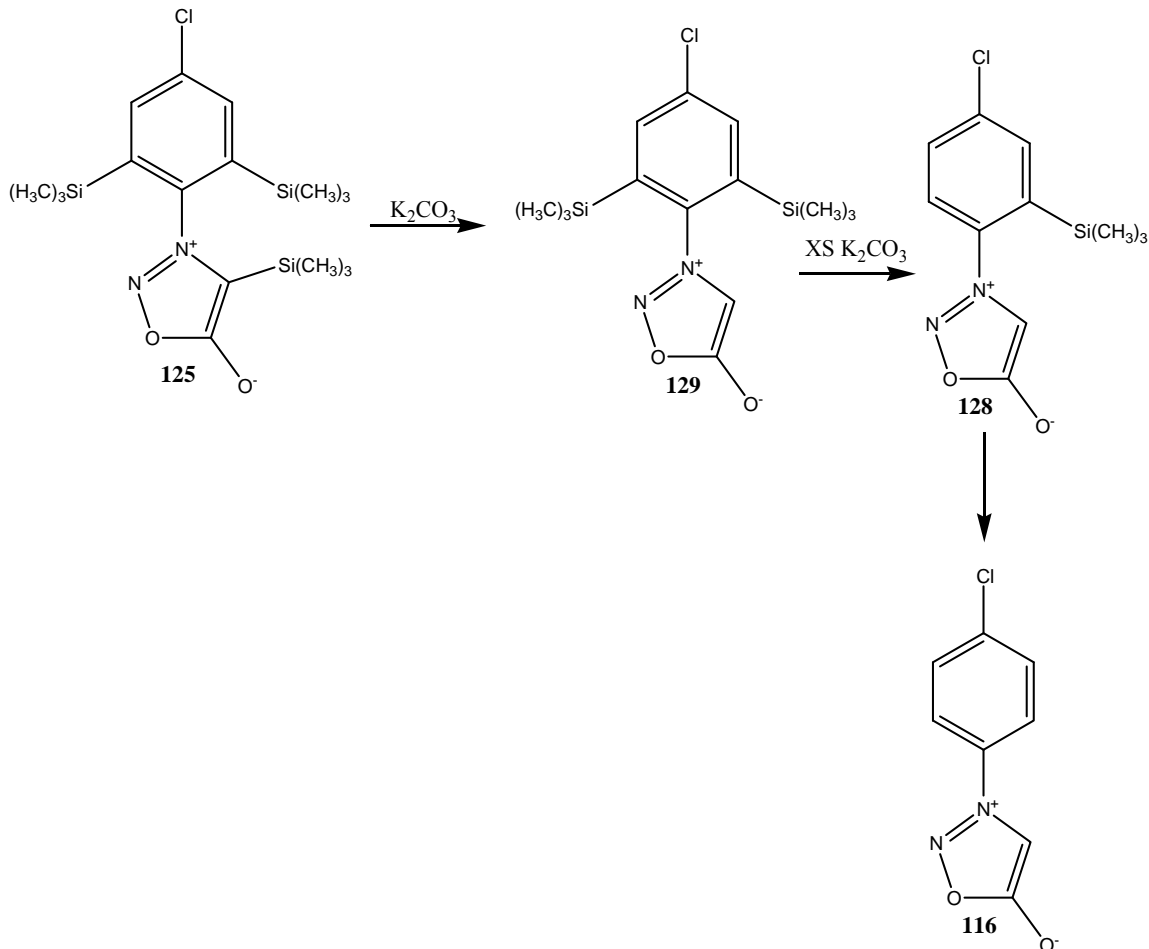
such the transformations shown in Scheme 29 were anticipated for 3-(4-chloro-2, 6-di(trimethylsilyl) phenyl)-4-trimethylsilylsydnone (**125**).

Scheme 29



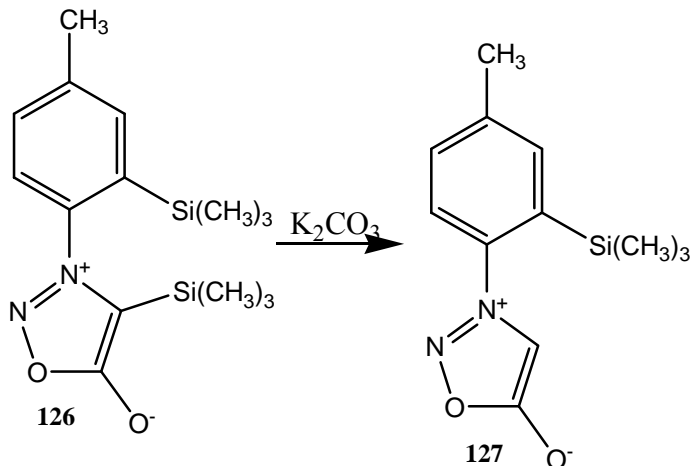
However, when the trisubstituted product **125** was treated with 3.5 equivalents of K_2CO_3 two lower running products (TLC) were isolated. It was thought that these two products could be the monosubstituted product **128** and the disubstituted product **129**. Indeed when the two products were compared to the authentic material (TLC and IR) they were shown to be the same (65% and 29%, respectively). As a follow up on this reaction, it was elected to attempt the reaction of **129** with 2.8 equivalents of K_2CO_3 , and this resulted in the removal of both silyl groups from the aryl ring. A logical sequence that was proposed from these observations is shown in Scheme 30.

Scheme 30



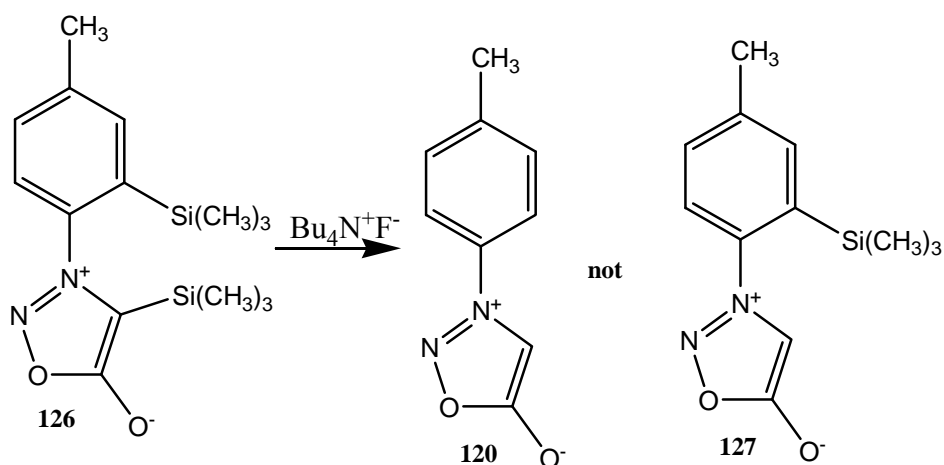
Armed with this observation, the next step was to attempt the desilylation of the disubstituted product **126**. As expected when **126** was treated with 2.35 equivalents of K_2CO_3 , the silyl group was selectively removed from the sydnone ring and the monosubstituted product **127** was obtained. It was then elected to make a follow up on the same reaction by treating the monosubstituted product **127** with 1.8 equivalents of K_2CO_3 and, as expected, no transformation was observed. Thus, selective transformation, as outlined in Scheme 31, had been successfully achieved.

Scheme 31



Next, it was then elected to try the same transformation using tetrabutylammonium fluoride ($\text{Bu}_4\text{N}^+\text{F}^-$). Unfortunately, treatment of **126** with 1 equivalent of $\text{Bu}_4\text{N}^+\text{F}^-$ could not achieve the desired selective desilylation. In fact both silyl groups, the *ortho* and the C-4 attached were removed as shown by comparison with authentic material (TLC, IR, NMR). Thus, the transformation shown below had been achieved and the same general trend was observed with **125**, **129** and **127**.

Scheme 32



The desilylation reactions of **125** and **126** with K_2CO_3 and $\text{Bu}_4\text{N}^+\text{F}^-$ are summarized in Tables 4 and 5 respectively.

Table 4 Reactions of 125,126,127 and 129 with K₂CO₃

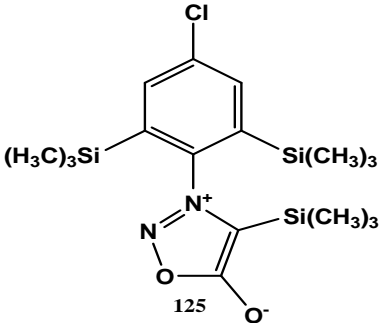
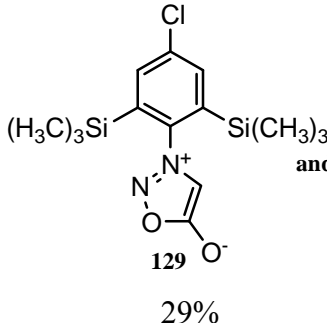
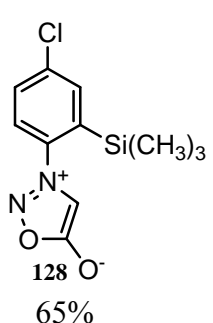
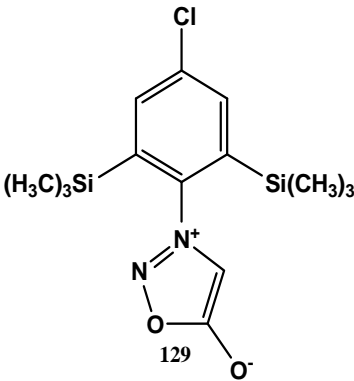
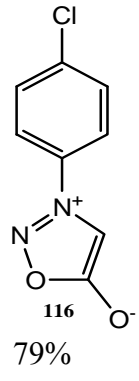
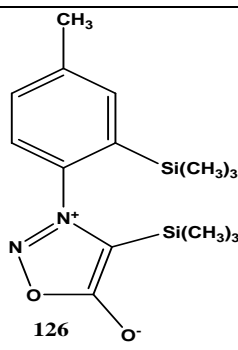
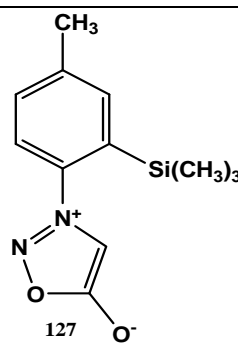
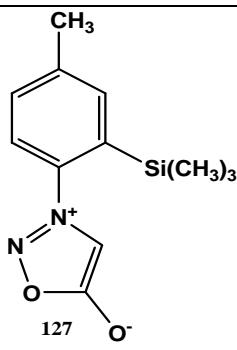
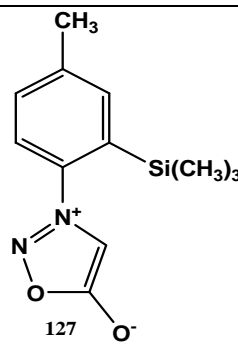
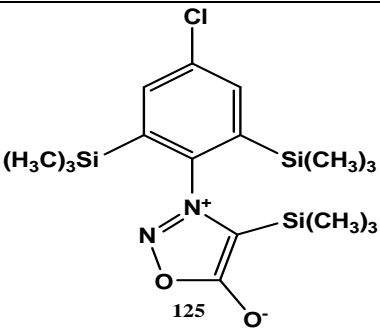
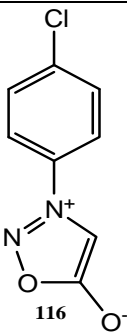
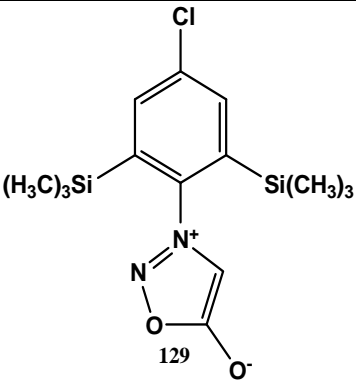
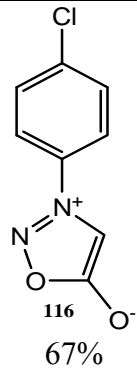
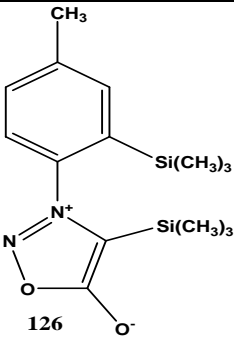
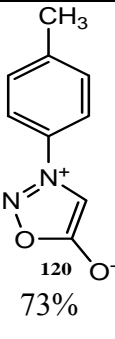
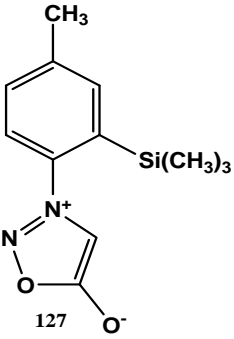
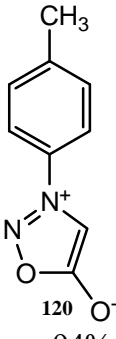
Starting material	Product / yield	Percentage of conversion (%)
 <p>125</p>	 <p>129</p> <p>29%</p> <p>and</p>  <p>128</p> <p>65%</p>	94
 <p>129</p>	 <p>116</p> <p>79%</p>	100
 <p>126</p>	 <p>127</p> <p>93%</p>	100
 <p>127</p>	 <p>127</p> <p>No reaction</p>	0

Table 5 Reactions of 125, 126, 127 and 129 with Bu₄N⁺F⁻

Starting material	Product / yield	Percentage of conversion (%)
 <p>125</p>	 <p>116</p> <p>84%</p>	100
 <p>129</p>	 <p>116</p> <p>67%</p>	100
 <p>126</p>	 <p>120</p> <p>73%</p>	100
 <p>127</p>	 <p>120</p> <p>94%</p>	100

In conclusion, diiodination of 3-(4-methylphenyl)sydnone and 3-(4-chlorophenyl)sydnone has been achieved in modest to good yields. The *ortho*-iodophenyl congeners were also produced in good yields by direct lithiation and reduction methods. Trisilylation and disilylation of the two sydnones was also achieved in modest yields. Selective desilylation was achieved with potassium carbonate, but the same could not be achieved with tertbutylammonium fluoride.

Experimental

All starting reagents were purchased from commercial sources and used without further purification. Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were acquired on a Mattson Genesis II FTIR. NMR spectra were acquired on a Bruker 300 MHz NMR and are reported in δ units or ppm relative to tetramethyl silane as internal standard. Elemental analyses were performed by Microlab LLC, Indianapolis, Indiana.

Synthesis of starting materials

Synthesis of N-(4-chlorophenyl) glycine (114, X=Cl)

4-chloroaniline (6.4g, 0.05mol), anhydrous sodium acetate (5g, 0.06mol) and ethyl bromoacetate (5.7ml, 0.05mol) were dissolved in ethanol (15mL) and heated to reflux at 110°C for 45minutes. The reaction was left to cool to room temperature, poured into water (50mL) and then filtered. The ester collected (8.6g) was left to dry overnight. It was then suspended in sodium hydroxide (20mL, 20%) and ethanol (2-3mL) was added. The reaction contents were then refluxed at 110°C for one hour, allowed to cool to room temperature and then acidified with 12% hydrochloric acid. The precipitate formed was then filtered and left to dry overnight. The glycine collected (5.2g, 55.8%) was identical to authentic material (TLC, IR, m.p.), m.p. 137-138°C. I.R. (KBr): 3021, 2946, 2917, 2811, 2701, 1901, 1562, 1513, 1382, 1319, 1232, 1191, 1105, 1039, 1002, 985, 867, 813, 728, 694, 566, 487, 453cm⁻¹.

Synthesis of N-(4-methylphenyl) glycine (114, X=CH₃)

Para-toulidene (5.4g, 0.05mol), anhydrous sodium acetate (5g, 0.06mol) and ethyl bromoacetate (5.7mL, 0.05mol) were dissolved in ethanol (15mL) and heated to reflux at 110°C for 45minutes. The reaction was left to cool to room temperature, poured into of water (50mL) and then filtered. The ester collected (8.28g) was left to dry overnight. It was then suspended in 20% sodium hydroxide (20mL) and ethanol (2-3mL) added. The reaction contents were then refluxed at 110°C for one hour, allowed to cool to room temperature and then acidified with 12% hydrochloric acid. The precipitate formed was

then filtered and left to dry overnight. The glycine collected (5.2g, 63%) was then compared with authentic material (TLC, IR, m.p.), m.p. 137-138°C.

IR: 3139, 1878, 1752, 1602, 1509, 1449, 1384, 1311, 1292, 1228, 1175, 1083, 1010, 947, 857, 817, 793, 727, 695, 596, 553, 493cm⁻¹.

Synthesis of 3-(4-chlorophenyl)sydnone (116)

N (4-chlorophenyl) glycine (5g, 0.027moles) was suspended in water (60mL) and cooled to 0°C. Sodium nitrite (2.2g, 0.032moles) dissolved in water (15mL) was then slowly added. This was left stirring at close to 0°C for 3hours. The almost clear solution obtained was then filtered quickly with suction, after which norit (15mg) was added and the solution stirred. The mixture was then filtered again and hydrochloric acid (5mL) added. This produced a profusion of light fluffy crystals. The suspension was stirred for 10 minutes and filtered with suction, washed twice with ice cold water and left to dry overnight.

The solids obtained were dissolved in dichloromethane (80mL) and cooled to 0°C.

Trifluoroacetic anhydride (7.3mL) was then added drop wise until a clear solution was obtained.

The reaction was transferred to a large petri-dish and the dichloromethane and trifluoroacetic anhydride allowed to evaporate in the fume hood. The remaining trifluoroacetic acid was then neutralized with 5% sodium bicarbonate. The solid was then filtered and washed with water twice and then left to dry overnight. The product was then columned to give reasonably pure material. The sydnone collected (3.5g, 66%) was then compared with authentic material (TLC, IR, mp, NMR), m.p. 110-112°C.

IR(KBr) 3112(sydnone C-H),1911, 1889, 1770 (sydnone C=O), 1733(sydnone C=O), 1592, 1492,1448, 1423,1384,1346,1280,1241, 1172, 1093,1022,1008,950,860,853,728, 507cm⁻¹

¹HNMR (CDCl₃): 7.75(d), 7.65(d), 6.8(s) [sydnone C-H] ppm

¹³CNMR: 93.70(sydnone C-H), 122.59, 130.58, 133.17, 138.77, 168.79(sydnone C=O) ppm

Synthesis of 3-(4-methylphenyl) sydnone (120)

N (4-methylphenyl) glycine (5g, 0.028moles) was suspended in water (60mL) and cooled to 0°C. Sodium nitrite (2.2g, 0.032moles) dissolved in water (15mL) was then slowly added. This was left stirring at close to 0°C for 3hours. The almost clear solution obtained was then filtered quickly with suction, after which norit (15mg) was added and the solution stirred. The mixture was then filtered again and hydrochloric acid (5mL) added. This produced a profusion of light fluffy crystals. The suspension was stirred for 10 minutes and filtered with suction, washed twice with ice cold water and left to dry overnight.

The solids obtained were dissolved in dichloromethane (80mL) and cooled to 0°C. Trifluoroacetic anhydride (7.3mL) was then added drop wise until a clear solution was obtained.

The reaction was transferred to a large petri-dish and the dichloromethane and trifluoroacetic anhydride allowed to evaporate in the fume hood. The remaining trifluoroacetic acid was then neutralized with 5% sodium bicarbonate. The solid was then filtered and washed with water twice and then left to dry overnight. The product was then

columned to give reasonably pure material. The sydnone collected (3.6g, 73%) was then compared with authentic material (TLC, IR, mp, NMR), m.p. 140-142°C.

IR:(KBr):3139(sydnone C-H) ,3052,2923,2852,2343,2115,2024,1889,1751(sydnone C=O),1508,1448,1384,1292,1226, 1174,1081,1010,946,856,817,792,727,694,595,533,493, 426cm⁻¹

¹HNMR:7.65(d), 7.35(d), 6.7(s) [sydnone C=O], 2.5ppm

¹³CNMR:20.76, 94.56(sydnone C-H), 121.19, 130.46, 132.21, 142.66, 168.48(sydnone C=O) ppm

Synthesis of iodosydnone

Synthesis of 3-(4-chloro-2-iodophenyl)-4-iodosydnone (118).

Under dry nitrogen conditions, the sydnone (100mg, 0.51mmol) was dissolved in dry THF (50mL) and cooled to -78°C in an acetone/dry ice bath. After 20 minutes, *n*-Butyllithium (1.1mL, 1.6M, 1.71mmole, 3.4eq.) was added dropwise. After an additional 50 minutes; iodine (324.4mg, 1.28mmoles) was then added quickly to the reaction. The reaction was left overnight after which the contents were poured into saturated brine (100mL) and left in the fume hood. After the THF had evaporated, the organic layer was extracted with dichloromethane (3x 50mL). The combined layers were then washed with 5% sodium sulfite (50mL) followed by a backwash with water. The golden yellow solution was then dried with magnesium sulfate and evaporated in vacuo. The product, a paste-like material, was then columned and recrystallized (dichloromethane/hexanes) to yield the pure crystals (122mg, 54%yield), m.p.178-180°C.

IR(KBr)2915,2852,1714(sydnone C=O),1589,1488,1446,1413,1384,1332,1286,1267,1203,1056,1039,1012,971,815,715,642,586 cm⁻¹

¹HNMR: 8.03(s), 7.55(d), 7.31(d) ppm

¹³CNMR: 52.96(sydnone C-I), 94.51, 128.16, 130.13, 136.65, 139.45, 140.28,
168.38(sydnone C=O) ppm

Synthesis of 3-(4-methyl-2-iodophenyl)-4-iodosydnone (122).

Under dry nitrogen conditions, the sydnone (100mg, 0.57mmol) was dissolved in dry THF (50mL) and cooled to -78°C in an acetone/dry ice bath. After 20 minutes, *n*-Butyl lithium (1.2mL, 1.6M, 1.94mmole, 3.4eq.) was added dropwise. After an additional 50 minutes; iodine (324.4mg, 1.28mmoles) was added quickly to the reaction. The reaction was left overnight after which the contents were poured into saturated brine (100mL) and left in the fume hood. After the THF had evaporated, the organic layer was extracted with dichloromethane (3x 100mL). The combined layers were then washed with 5% sodium sulfite (50mL) followed by a backwash with water. The golden yellow solution was then dried with magnesium sulfate and evaporated in vacuo. The product, a paste-like material, was then recrystallized (dichloromethane/hexanes) to yield the pure crystals (182mg, 75%yield), m.p. 188-190°C.

IR(KBr): 3083, 2922, 2344, 1708(sydnone C=O), 1637, 1570, 1474, 1411, 1384, 1328,
1256, 1200, 1101, 1053, 1012, 972, 819 cm⁻¹

¹HNMR: 7.89(s), 7.43(d), 7.23(d) ppm

¹³CNMR: 21.04, 53.03(sydnone C-I), 93.51, 124.79, 127.01, 130.43, 141.06, 144.84,
168.60(sydnone C=O) ppm

Elemental Analysis Calculated for C₉H₆I₂N₂O₂ (Mol.wt: 427.97): C, 25.26; H, 1.41; I, 59.31; N, 6.55; O, 7.48; Found: C: 25.56, H: 1.86, N: 6.34

Synthesis of 3-(4-chloro-2-iodophenyl)sydnone (119)

Under dry nitrogen conditions, the sydnone (500mg, 2.54mmol) was dissolved in dry THF (100mL) and cooled to -78°C in an acetone/ether/dry ice bath. After 30 minutes, *n*-Butyllithium (3.25mL, 2.5M, 8.13mmole, 3.2equiv.) was added dropwise. After an additional 1.5 hours, iodine (1.6g, 6.3mmoles, 2.2equiv.) was added quickly to the reaction. The reaction was left for 3 hours after which the contents were poured into saturated brine (100mL) and left in the fume hood.. After the THF had evaporated, the organic layer was extracted with dichloromethane (3x 100mL).The combined layers were then washed with 5% sodium sulfite (50mL) followed by a backwash with water. The golden yellow solution was then dried with magnesium sulfate and evaporated in vacuo. The product, a paste-like material, was then columned and recrystallized in (dichloromethane/hexanes) to yield the pure crystals (650mg, 49%), m.p.176-178°C.

IR (KBr): 3140 (sydnone C-H), 1728(sydnone C=O), 1572, 1479,1437,1383,1097,937, 854, 820ppm

¹HNMR (CDCl₃):7.99(s), 7.52(d), 7.36(d), 6.48(s) [sydnone C-H] ppm

¹³CNMR (DMSO):95.99, 98.87, 128.45, 129.70, 136.50, 137.53, 139.06, 168.22(sydnone C=O) ppm

Synthesis of 3-(4-methyl-2-iodophenyl)sydnone (123)

Under dry nitrogen conditions, the sydnone (500mg, 2.84mmol) was dissolved in dry THF (100mL) and cooled to -78°C in an acetone/ether/dry ice bath. After 30 minutes, *n*-Butyllithium (3.65mL, 2.5M, 9.01mmole, 3.2equiv.) was added dropwise. After an additional 1.5 hours, iodine (1.6g, 6.3mmoles, 2.2equiv.) was added quickly to the

reaction. The reaction was left for 2.5 hours after which the contents were poured into saturated brine (100mL) and left in the fume hood. After the THF had evaporated, the organic layer was extracted with dichloromethane (3x 100mL). The combined layers were then washed with 5% sodium sulfite (50mL) followed by a backwash with water. The golden yellow solution was then dried with magnesium sulfate and evaporated in vacuo. The product, a paste-like material, was then columned and recrystallized (dichloromethane/hexanes) to yield the pure crystals (580mg, 68%). m.p. 133-135°C IR:(KBr):3137(sydnone C-H),1730(sydnone C=O),1590,1492,1447,1384,1355, 1265,1232,1168,1094,1054, 1002,937,857,817,731,702,597,572,502cm⁻¹. ¹HNMR (CDCl₃):2.45(d), 6.52(s)[sydnone C-H], 7.28(d), 7.38(d), 7.87(s)ppm ¹³CNMR (CDCl₃):21.03, 91.60, 97.71, 126.31, 127.01, 130.27, 130.43, 141.05, 141.28, 144.64, 168.68(sydnone C=O) ppm

Synthesis of trimethylsilylsydnone

Synthesis of 3-(4-chloro-2, 6-di(trimethylsilyl) phenyl)-4-trimethylsilylsydnone (125)

Under dry nitrogen conditions, the sydnone (100mg, 0.51mmoles) was dissolved in dry THF (50mL) and cooled to -78°C in an acetone/dry ice bath. After 20 minutes, n-Butyllithium (1.3mL, 2.24 mmole) was added dropwise. After an hour, chlorotrimethyl silane. (0.2mL, 1.53mmoles) was slowly added to the reaction. The reaction was left overnight after which the contents were poured into saturated brine (50mL) and left in the fume hood. After the THF had evaporated, the organic layer was extracted with dichloromethane (3x 50mL). The combined layers were then washed with 5% sodium sulfite (50mL) followed by a backwash with water. The golden yellow solution was then

dried with magnesium sulfate and evaporated in vacuo. The product, brown oil, was then columned to give reasonably pure solid material (63mg, 30%), m.p. 156-158°C.

IR(NaCl): 2920, 2850, 1733 (sydnone C=O), 1545, 1509, 1462, 1412, 1375, 1256, 1212, 1125, 1072, 1040, 956, 848, 764, 700, 627 cm⁻¹

¹HNMR (CDCl₃): 7.35(s), 0.0(s), -0.15(s) ppm

¹³CNMR (CDCl₃): -0.52, -0.38, 109.89, 133.53, 137.04, 137.78, 141.64, 142.91, 173.64 (sydnone C=O)

Elemental Analysis Calculated for C₁₇H₂₉ClN₂O₂Si₃ (Mol.wt: 413.13): C, 49.42; H, 7.08; Cl, 8.58; N, 6.78; O, 7.75; Si, 20.39 Found: C: 46.06, H: 6.53, N: 6.28

Synthesis of 3-(4-chloro-2, 6-di(trimethylsilyl) phenyl) sydnone (129)

Under dry nitrogen conditions, the sydnone (400mg, 2.03mmoles) was dissolved in dry THF (100mL) and cooled to -78°C in an acetone/ether/dry ice bath. After 30 minutes, (3.0mL, 2.5M, 7.51 mmole, 3.7eq) of *n*-Butyllithium was added dropwise. After 30 minutes, chlorotrimethylsilane (0.7mL, 5.5mmoles) was slowly added to the reaction.

The reaction was left for 2 hours after which the contents were poured into saturated brine (100mL) and left in the fume hood. After the THF had evaporated, the organic layer was extracted with dichloromethane (3x 100mL). The golden yellow solution was then dried with magnesium sulfate and evaporated in vacuo. The product, brown oil, was then columned to give reasonably pure solid material (140mg, 20% yield) m.p. 134-136°C

IR(NaCl): 3144 (sydnone C-H), 3041, 2959, 1860, 1747 (sydnone C=O), 1544, 1454, 1414, 1369, 1348, 1254, 1207, 1168, 1127, 1070, 1021, 1000, 932, 841, 772, 758, 734, 695 cm⁻¹

¹HNMR: 0.00(s), 7.50(s), 7.60(s) ppm

¹³CNMR: 0.00, 102.41, 137.25, 137.68, 140.97, 142.86, 168.95 (sydnone C=O) ppm

Elemental Analysis Calculated for $C_{14}H_{21}ClN_2O_2Si_2$ (Mol.wt:340.95): C, 49.32; H, 6.21; Cl, 10.40; N, 8.22; O, 9.39; Si, 16.47 Found: C, 47.53; H, 6.24; N, 7.98

Synthesis of 3-(4-chloro-2-trimethylsilylphenyl) sydnone (128)

Under dry nitrogen conditions, the sydnone (400mg, 2.03mmoles) was dissolved in dry THF (100mL) and cooled to $-78^{\circ}C$ in an acetone/ether/dry ice bath. After 30 minutes, (3.0mL, 2.5M, 7.51 mmole, 3.7eq) of *n*-Butyllithium was added dropwise. After 30 minutes, chlorotrimethylsilane. (0.7mL, 5.5mmoles) was slowly added to the reaction. The reaction was left for about 2 hours after which the contents were poured into saturated brine (100mL) and left in the fume hood. After the THF had evaporated, the organic layer was extracted with dichloromethane (3x 100mL), followed by a backwash with water. The golden yellow solution was then dried with magnesium sulfate and evaporated in vacuo. The product, brown oil, was then columned to give reasonably pure solid material (108mg, 20%yield), m.p. $64-66^{\circ}C$.

IR(NaCl) 3116(sydnone C-H), 2967, 1741(sydnone C=O), 1555, 1441, 1376, 1248, 1221, 1146, 1106, 1072, 1003, 934, 894, 835, 761, 730, 684 cm^{-1}

1H NMR (DMSO): 0.00(s), 7.42(s) [sydnone C-H], 7.62(d) ppm

^{13}C NMR (DMSO): 0.00, 100.13, 128.83, 131.87, 136.61, 137.97, 138.98, 139.74, 169.27(sydnone C=O) ppm

Elemental Analysis Calculated for $C_{11}H_{13}ClN_2O_2Si$ (Mol.wt:268.77): C, 49.16; H, 4.88; Cl, 13.19; N, 10.42; O, 11.91; Si, 10.45 Found: C, 49.44; H, 4.99; N, 10.10

Synthesis of 3(4-methyl-2-trimethylsilylphenyl)-4-trimethylsilylsydnone (126)

Under dry nitrogen conditions, the sydnone (200mg, 1.168mmoles) was dissolved in dry THF (100mL) and cooled to $-78^{\circ}C$ in an acetone/dry ice bath. After 15 minutes, (2.9mL,

1.6M, 4.67mmole, 4eq) of *n*-Butyllithium was added dropwise. After an hour, chlorotrimethyl silane. (0.43mL, 3.39mmoles) was slowly added to the reaction. The reaction was left for about 4 hours after which the contents were poured into saturated brine (100mL) and left in the fume hood. After the THF had evaporated, the organic layer was extracted with dichloromethane (3x 100mL), followed by a backwash with water. The golden yellow solution was then dried with magnesium sulfate and evaporated in vacuo. The product, brown oil, was then columned to give reasonably pure material (148mg, 40% yield) , m.p.78-80°C.

IR:3046,2958,2925,2900,1737(sydnone C=O),1573,1484,1403,1251,1155,1085,1039,966,838,759,694,634,590cm⁻¹

¹HNMR (CDCl₃):-0.10(s), 0.00(s), 2.30(s), 7.01(d), 7.15(d), 7.30(s)ppm

¹³CNMR(CDCl₃):0.84,0.00,22.24,106.98,126.66,131.15,137.43,137.87,139.02,142.15,174.19ppm Elemental Analysis Calculated for C₁₅H₂₄N₂O₂Si₂ (Mol.wt:320.53): C, 56.21; H, 7.55; N, 8.74; O, 9.98; Si, 17.52 Found: C: 56.86, H: 7.55, N: 8.44

Synthesis of 3-(4-methyl-2-trimethylsilylphenyl) sydnone (127)

Under dry nitrogen conditions, the sydnone (400mg, 2.28mmoles) was dissolved in dry THF (100mL) and cooled to -78°C in an acetone/ether/dry ice bath. After 20 minutes, (4.0ml, 2.5M, 10.03mmole, 4.4eq.) of *n*-Butyllithium was added dropwise. After 2.5 hours, chlorotrimethyl silane. (1.16mL, 9.12mmoles) was slowly added to the reaction. The reaction was left for about 2.5 hours after which the contents were poured into saturated brine (100mL) and left in the fume hood. After the THF had evaporated, the organic layer was extracted with dichloromethane (3x 100mL). followed by a backwash

with water. The golden yellow solution was then dried with magnesium sulfate and evaporated in vacuo. The product, brown oil, was then columned to give reasonably pure material (243mg, 43% yield), m.p. 74-76°C.

IR(NaCl): 3130(sydnone C-H), 2954, 1749(sydnone C=O), 1578, 1487, 1443, 1384, 1359, 1288, 1250, 1220, 1168, 1144, 1099, 1072, 1039, 1006, 936, 879, 842, 765 cm⁻¹

¹H NMR (CDCl₃): 0.00(s), 2.26(s), 6.29(s) [sydnone C-H], 7.07(d), 7.15(d), 7.29(s) ppm

¹³C NMR: 0.00, 21.71, 99.50, 126.19, 132.04, 135.93, 137.29, 137.86, 142.42, 169.16(sydnone C=O) ppm

Reduction of iodosydnone

Reduction of 3-(4-methyl-2-iodophenyl)-4-iodosydnone (122) with sodium borohydride

The diiodinated sydnone (50mg, 0.117mmoles) was dissolved in 2mL methanol. Sodium Borohydride (150mg, 3.97mmoles) was then added in portions while the reaction was monitored by TLC. After all the starting material was gone the methanol was allowed to evaporate in the fume hood. About 2-3mL of water was then added and an insoluble solid was obtained. The product (18mg, 87% yield) was obtained after filtration, m.p. 140-142°C.

IR: 3139(sydnone C-H), 3052, 2923, 2852, 2343, 2115, 2024, 1889, 1751(sydnone C=O), 1508, 1448, 1384, 1292, 1226, 1174, 1081, 1010, 946, 856, 817, 792, 727, 694, 595, 533, 493 cm⁻¹

¹H NMR: 7.65(d), 7.35(d), 6.7(s) [sydnone C=O], 2.5 ppm

¹³C NMR: 20.76, 94.56(sydnone C-H), 121.19, 130.46, 132.21, 142.66, 168.48(sydnone C=O) ppm

Reduction of 3-(4-methyl-2-iodophenyl)-4-iodosydnone (122) with Sodium sulfite

The diiodinated sydnone (50mg, 0.117mmoles) was dissolved in 2mL methanol. Sodium Sulfite (50mg, 0.4mmole) dissolved in about 2mL of water was then added. The reaction was then allowed to go while being monitored by TLC. After all the starting material had gone the methanol was allowed to evaporate in the fume hood. The resulting mixture was then extracted three times with dichloromethane (3x20mL). The combined extracts were then washed with water (50mL) dried with Magnesium sulfate and evaporated in vacuo. The crude products were then columned to give the pure product (30mg, 85% yields), m.p. 133-135°C.

IR(KBr): 3137(sydnone C-H), 1730(sydnone C=O), 1590, 1492, 1447, 1384, 1355, 1265, 1232, 1168, 1094, 1054, 1002, 937, 857, 817, 731, 702, 597, 572, 502 cm⁻¹.

¹H NMR (CDCl₃): 2.45(d), 6.52(s) [sydnone C-H], 7.28(d), 7.38(d), 7.87(s) ppm

¹³C NMR (CDCl₃): 21.03, 91.60, 97.71, 126.31, 127.01, 130.27, 130.43, 141.05, 141.28, 144.64, 168.68(sydnone C=O) ppm

Reduction of 3-(4-chloro-2-iodophenyl)-4-iodosydnone (118) with sodium borohydride

The diiodinated sydnone (50mg, 0.117mmoles) was dissolved in methanol (2mL). Sodium borohydride (150mg, 3.97mmoles) was then added in portions while the reaction was monitored (TLC). After all the starting material was gone the methanol was allowed to evaporate in the fume hood. Water (2-3mL) was then added and an insoluble solid was obtained. The product (18mg, 87% yield) was obtained after filtration, m.p. 110-112°C.

IR:3112(sydnone C-H),1911,1889,1770(sydnone C=O),1733(sydnone C=O),1592,1492,1448,1423,1384,1346,1280,1241,1172,1093,1022,1008,950,860,853,728,507cm⁻¹

¹HNMR 7.75 (d), 7.65(d), 6.8(s) ppm

¹³CNMR: 93.70, 122.59, 130.58, 133.17, 138.77, 168.79(sydnone C=O) ppm

Reduction of 3-(4-chloro-2-iodophenyl)-4-iodosydnone (118) with Sodium sulfite

The diiodinated sydnone (50mg, 0.117mmoles) was dissolved in methanol (2mL). Sodium Sulfite (50mg ,0.4mmole) dissolved in water (2mL) was then added .The reaction was then allowed to go while being monitored (TLC).After all the starting material had gone the methanol was allowed to evaporate in the fume hood. The resulting mixture was then extracted with dichloromethane (3x20mL).The combined extracts were then washed with water (50mL), dried with magnesium sulfate and evaporated in vacuo. The crude products were then columned to give the pure product (30mg, 85% yield), m.p.176-178°C.

IR:3140(sydnone C-H),1728(sydnone C=O),1572,1479,1437,1383,1097,937,854,820ppm

¹HNMR (CDCl₃):7.99(s), 7.52(d), 7.36(d), 6.48(s) [sydnone C-H] ppm

¹³CNMR (DMSO):95.99, 98.87, 128.45, 129.70, 136.50, 137.53, 139.06, 168.22[sydnone C=O] ppm

Attempted selective desilylation of trimethylsilylsydnones

General procedure for desilylation with potassium carbonate

To the silylsydnone compound in methanol: methylene chloride (3:1) was added 1-3.5 eq. potassium carbonate. After stirring for 3hours, the reaction mixture was added to water (10mL), and extracted with methylene chloride (3×10mL). The combined extracts were dried (MgSO₄) and evaporated in *vacuo* to yield the crude desilylated

product, which was columned (hexane/ methylene chloride) and then recrystallized from methylene chloride / hexane.

General procedure of desilylation with tetrabutylammonium fluoride

To the silylsydnone compound (~50mg) in dry THF (5mL) was added tetrabutylammonium fluoride (1.0 eq.) dropwise under nitrogen. After for 15minutes, the reaction mixture was added to water (10mL), and extracted with methylene chloride (3×10mL). The combined extracts were dried (MgSO₄) and evaporated in *vacuo* to yield the crude desilylated product, which was columned (hexane/methylene chloride) and then recrystallized from methylene chloride / hexane.

Desilylation with potassium carbonate

Selective desilylation of 3-(4-chloro-2, 2'-(trimethylsilyl) phenyl)-4-

trimethylsilylsydnone (125)

Using the general procedure, the trimethylsilylsydnone **125**(0.041g, 0.10mmol) was treated with K₂CO₃ (48.5mg, 0.35mmoles) and afforded the crude desilylated products together with some starting material (~33mg total weight) which were later separated to give pure materials **128** (17.5mg, 65%) and **129**(10mg, 29%) identical to authentic sample by TLC and IR.

Attempted desilylation of 3-(4-chloro-2, 2'-(trimethylsilyl) phenyl) sydnone (129)

Using the general procedure, the disilylsydnone **129** (0.100g, 0.29mmol) was treated with K_2CO_3 (130mg, 0.81mmoles) and afforded the desilylated product **116** (45.5mg, 79%) after purification, m.p.110-112°C.

IR(KBr)3112.56,1911.12,1889.90,1770.34,1733.70,1592.92,1492.64,1448.28,1423.21,1384.64,1346.07,1280.51,1241.94,1172.51,1093.44,1022.09,1008.59,950.74,860.10,853.03, 728.96,507.19 cm^{-1}

1H NMR ($CDCl_3$): 7.75(d), 7.65(d), 6.8(s) ppm

^{13}C NMR: 93.70, 122.59, 130.58, 133.17, 138.77, 168.79ppm

Selective desilylation of 3(4-methyl-2-trimethylsilylphenyl)-4-trimethylsilylsydnone (126)

Using the general procedure, the disilylsydnone**126** (0.050g, 0.16mmol) was treated with K_2CO_3 (52mg, 0.38mmoles) and afforded the desilylated product **127** (37mg, 93%) after purification, m.p.74-76°C.

IR:3130,2954,1749,1578,1487,1443,1384,1359,1288,1250,1220,1168,1144,1099,1072,1039,1006,936,879,842,765 cm^{-1}

1H NMR ($CDCl_3$):0.00(s), 2.26(s), 6.29(s) [sydnone C-H], 7.07(d), 7.15(d), 7.29(s) ppm

^{13}C NMR:0.00, 21.71, 99.50, 126.19, 132.04, 135.93, 137.29, 137.86, 142.42, 169.16ppm

Attempted desilylation of 3(4-methyl-2-trimethylsilylphenyl) sydnone (127)

Using the general procedure, the monosilylsydnone **127** (0.100g, 0.40mmol) was treated with K_2CO_3 (130mg, 0.81mmoles and afforded the desilylated product **127** (0.100g, 100%) after purification, identical to authentic sample by TLC and IR.

Desilylation with tetrabutylammonium fluoride

Attempted selective desilylation of 3-(4-chloro-2, 2'-di(trimethylsilyl) phenyl)-4-trimethylsilylsydnone (125)

Using the general procedure, the trimethylsilylsydnone **125** (0.050g, 0.12mmol) afforded the desilylated product **116** (19.8mg, 84%) after purification, identical to authentic sample by TLC and IR.

Attempted desilylation of 3-(4-chloro-2, 2'-(trimethylsilyl) phenyl) sydnone (129)

Using the general procedure, the disilylsydnone **129** (0.045g, 0.15mmol) afforded the desilylated product **116** (19.7mg, 67%) after purification identical to authentic sample by TLC and IR.

Attempted desilylation of 3(4-methyl-2-trimethylsilylphenyl)-4-trimethylsilylsydnone (126)

Using the general procedure, the disilylsydnone **126** (0.042g, 0.13mmol) afforded the desilylated product **120** (16.7mg, 73%) after purification identical to authentic sample by TLC and IR.

Attempted desilylation of 3(4-methyl-2-trimethylsilylphenyl) sydnone (127)

Using the general procedure, the monosilylsydnone **66** (0.065g, 0.26mmol) afforded the desilylated product **74** (43mg, 94%) and after purification identical to authentic sample by TLC and IR.

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